A. M. A.
ARCHIVES OF
NEUROLOGY AND PSYCHIATRY

JANUARY 1954
VOLUME 71, NUMBER 1

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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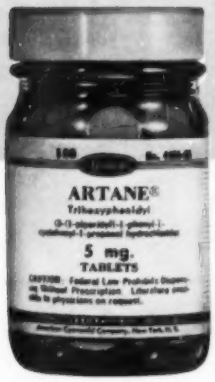

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Archives of Neurology and Psychiatry

VOLUME 71 JANUARY 1954 NUMBER 1

CONDUCTION OF PAIN IN MAN

Observations on Its Afferent Pathways Within the Spinal Cord and Visceral Nerves

JAMES C. WHITE, M.D.
BOSTON

HUGHLINGS JACKSON, in whose memory we are gathered this evening, had little to say about pain, but he was profoundly interested in what he termed impressions at the higher cortical level. He had this to say about the spinal cord:[1]

> But such facts as that the cord has certain sized and certain shaped columns of white matter and certain shaped areas of grey matter are facts of morphology. So, too, are facts as to the course of fibres and arrangements of cells disclosed by microscopical examination. The latter is not minute anatomy, but minute morphology; and however minute it becomes it does not turn into physiology. It is only when the shapes of cells and course of fibres, etc. are shown to be subservient to the reception or conduction of particular impressions . . . that morphology ceases or rises into anatomy.

Here he has suggested just what we have been attempting in the work I am to discuss, though today we should call the investigation of pain conduction in conscious man "physiology." We have been developing a method of gaining a better understanding of function in the human cord and visceral plexuses from their ability, when stimulated, to receive and conduct impressions of pain. Also, approaching the problem in another way, my colleagues and I have studied the effects produced on somatic and visceral sensibility by surgical interruption of the spinal pain tracts and paravertebral sympathetic pathways.

MATERIAL AND METHODS FOR TESTING PAIN CONDUCTION

Our material from which conclusions regarding pain transmission can be drawn comprises a series of well over 300 anterolateral chordotomies and 200 sympathectomies. Additional details concerning the first 210 chordotomies have already been published in an article with Sweet, Hawkins, and Nilges,[2] and those concerning the sympathectomies, in a book with Smithwick and Simeone.[3] These operations have for the most part been performed on the neurosurgical service at the Massachusetts General Hospital, with a small proportion carried out in the United States Naval Hospitals at Chelsea, Mass., and St. Albans, N. Y., the Veterans Administration Hospital, at Framingham, Mass., and the Queen Elizabeth Hospital in Birmingham, England.

Following Dr. Wilder Penfield's example, we are attempting to study neurophysiology at every operation for the relief of pain by stimulation and observation of responses in conscious patients. It is no longer necessary to perform the entire exposure of the spinal cord, its roots, or the sympathetic structures with use of

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The Hughlings Jackson Lecture, given at the Montreal Neurological Institute, May 13, 1953. From the Neurosurgical Service of the Massachusetts General Hospital.

local anesthesia, as the patient can be kept lightly anesthetized with small amounts of intravenous thiopental (Pentothal), supplemented with nitrous oxide or trichloroethylene (Trilene), and then be awakened for testing. When this is done, approximately three subjects out of four prove, after a brief period, to be cooperative, intelligent witnesses. All have been told beforehand the purpose of the test, that it will increase the chance of success of their own operation, as well as help in the relief of other sufferers. When the desired tests have been completed, the patient can again be put to sleep. On awakening after the operation, many have no recollection of the procedure, and none have complained of undue discomfort.

In recent years we have attempted at every chordotomy to evaluate the level of analgesia,* information which is so vital if the operation is to be effective, and also, whenever circumstances permit, to test pain conduction in the tracts of the spinal cord. Similarly, we have studied pain evoked by stimulation of thoracic and lumbar ganglia or of the splanchnic nerves in the course of sympathectomies, whenever the pleura has been preserved intact and the patient is not a poor risk because of coronary disease.

For stimulation of fibers within the spinal cord, as well as for sympathetic structures, we have used fine bipolar gold-plated needle electrodes. These have been made by the Grass Instrument Company, of Quincy, Mass., with straight and right-angled tips. Stimulation is usually effective with a 1- to 3-volt signal, using a square wave of 1 msec. duration and 30 to 60 cps frequency.

PAIN TRANSMISSION IN SPINAL CORD

Since Spiller's [4] classical case of loss of pain and temperature sensation in both legs with preservation of tactile sensibility and motor power, which was shown at autopsy to result from solitary tubercles situated in each anterolateral column, all evidence has pointed to the importance of the ventral half of the spinal cord in the conduction of pain. The spinothalamic tract, however, is, unfortunately, not confined to a small bundle of fibers, as illustrated by Ranson and Clark [5] (Fig. 1). Many neurosurgeons, Loyal Davis,[6] for example, consider this to be the case and believe, as Frazier [7] first claimed, that analgesia can be obtained by making a 3-mm.-deep incision between the dentate ligament and the line of emergence of the ventral roots. That this is often not the case has been proved by many reports (Olivecrona,[8] Walker,[9] Hyndman and Van Epps,[10] Kahn and Peet,[11] Nulsen and Grant†) and by postmortem evidence from one of our patients. In Figure 2 is shown a spinal incision from the dentate ligament to the ventral root, penetrating to the central gray matter. This resulted only in hypalgesia to the costal margin and did not relieve pain in the thigh, caused by carcinomatous metastases.

* Analgesia is an important term to define. It means total inability to tell that a stimulus is sharp or painful. Mere pricking with a pin is not a suitable test, because some astute observers can tell the point from a blunt object by the small area of skin compressed. Others with high-grade hypalgesia will not report a single prick as painful. The best way to proceed is to test alternately with the blunt tip of a finger and the finger plus the protruding tip of a sharp needle, jabbing the skin vigorously with each stimulus. Any awareness that finger plus pin is different from finger tip alone, even if it gives rise to no actual pain, means that analgesia is not complete. Even with high-grade hypalgesia, pain from disease may still be present, and a more extensive chordotomy may relieve it.

† Personal communication to the author, 1953.

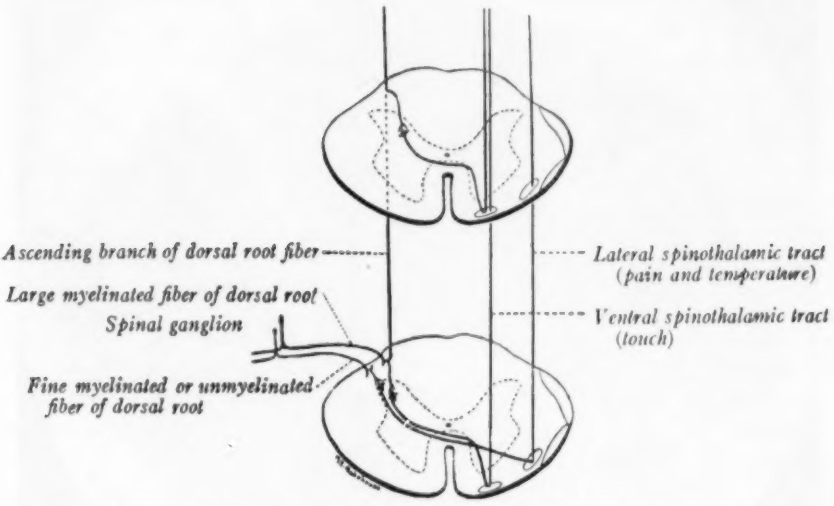

Fig. 1.—Position and extent of spinothalamic tract as illustrated by Ranson and Clark.[5]

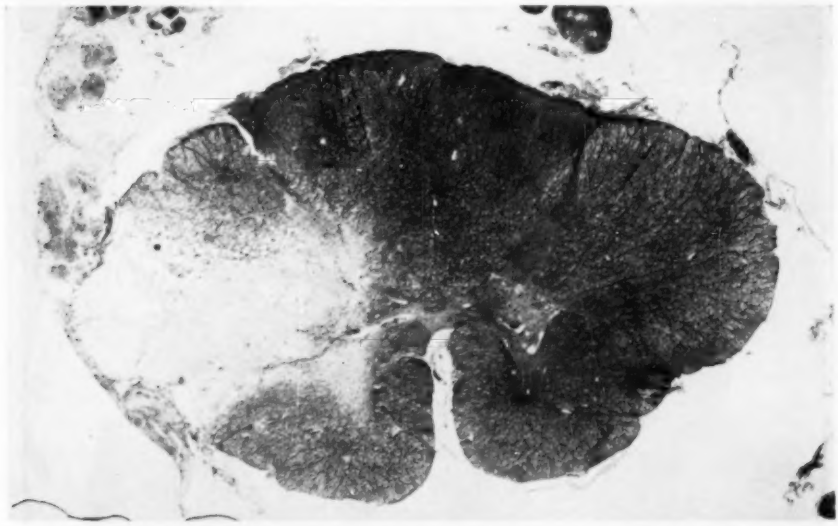

Fig. 2 (Patient G. B.).—Anterolateral incision from dentate ligament to ventral root. Although this chordotomy at T4 was carried much deeper than the 2.5-mm. cut recommended by Davis [6] and many others, it failed to relieve pain in the thigh. Hypalgesia extended to the T8 dermatome, but there was only patchy analgesia. No impairment of motor control was noted in either the ipsilateral leg or the bladder.

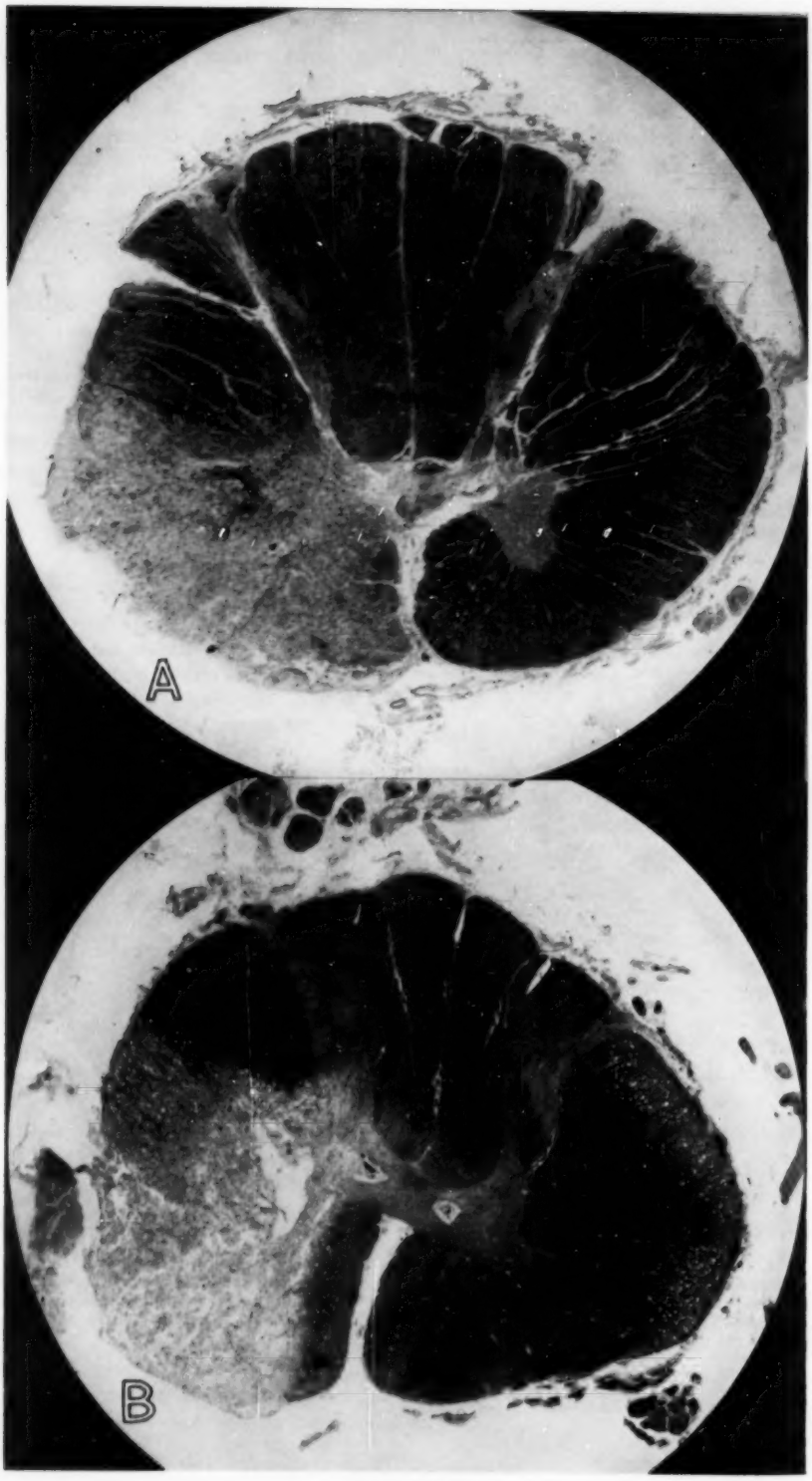

Figure 3

(See legends on opposite page)

Two lesions which caused complete analgesia and eliminated lower abdominal pain are shown in Figure 3. Although both cuts at the second thoracic segment have virtually transected the entire anterolateral quadrant, the more extensive (*A*) carried analgesia only to the umbilicus (with hypalgesia to the nipple line), while the somewhat less medial section (*B*) resulted in a maximal extent of analgesia to the fourth rib. Such discrepancies after roughly comparable transections can only be accounted for by variations in the number of segments required for the decussation of secondary axons conducting pain.

This level of decussation may be so high that two upper thoracic chordotomies, reported by French and Peyton [12] and Voris,[13] gave rise to only ipsilateral analgesia. In a patient of Dr. Sweet's a previous anterolateral chordotomy on the right at the second thoracic vertebra in another hospital had yielded analgesia on the left side to the seventh rib, except for the anoperineal region and the medial portion of the buttock. Pain persisted in this hypalgesic area. When Dr. Sweet widely reincised the upper thoracic cord, he failed to alter the zone of sacral sparing or to mitigate the pain. At a second trial electrical stimulation by means of our special microelectrode, inserted 2 mm. ventral to the dentate ligament to a depth of 2 mm. on the painful side, caused tingling paresthesiae in the ipsilateral knee. With this evidence for the presence of some uncrossed pain fibers, an extensive section of the anterolateral column was made at the first thoracic segment on the painful side. After this, in addition to contralateral analgesia on the right to T4, the sacral segments on the ipsilateral (left) side became analgesic as well, and the patient then remained free of pain for the remaining five months of his life.

Electrical stimulation within the anterolateral columns of the cord has given us interesting data in a number of other operations. This was first reported by Sweet, White, Selverstone, and Nilges.[14] Electrodes were inserted 1, 2, and 3 mm. anterior to the plane of the dentate ligament and to depths varying from 1 to 5 mm. Square waves of 30 cps frequency and 1-msec. duration were generally effective in eliciting a sensory response at potentials from 1 to 3 volts. Responses obtained from 200 stimulations in 23 cooperative patients have been recorded. The sensations evoked were pain, in 54%, and thermal sensations of heat, in 37%, and of cold, in the remaining 9%. In a general way, the deeper and more ventral the electrodes are inserted, the higher in the body the response is elicited. There is no tendency for the painful sensations to disappear as the electrodes are inserted 5 mm. to the most medial and ventral positions. At these points near the midline the pain may be referred ipsilaterally or to both sides simultaneously. A surprising feature of these responses to electrical stimulation is that pain was felt on the ipsilateral side in 12% and on both sides of the body in 6%. There is a distinct tendency for these uncrossed fibers to be concentrated near the midline. Axons conducting sensations of heat and

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EXPLANATION OF FIGURE 3

Fig. 3.—Two chordotomies with more radical transection of the anterolateral column.

A (Patient M. B.) Incision at T3 spinal segment: This very complete quadrant section produced full analgesia only to the umbilicus, although hypalgesia extended up to the xiphoid (T6). Leg and bladder control was not impaired.

B (Patient E. A.) Incision at T2 spinal segment: Analgesia and thermanesthesia here extended to above the nipple line (T4). Although the incision appears to involve the pyramidal fibers dorsal to the dentate ligament, there was no complicating paralysis of the leg or bladder.

cold seem to be intermingled with those transmitting pain and are not concentrated in any particular portion of the anterolateral column, as Foerster and Gagel [15] indicated.

In a typical case of Dr. Sweet's (Mary B., NECH #49-701) stimulation of the left anterolateral quadrant was carried out at different depths in a plane just anterior to the dentate ligament. This patient was under local anesthesia, and fully responsive, and gave an accurate description of her sensations. With the Grass stimulator yielding square waves of 1-msec. duration, 30-cps frequency, and 1-volt intensity, the patient noticed the following effects: at depth of 1 mm., severe pain in right leg up to knee; at depth of 2 mm., pain from right sole to right hip; at depth of 3 mm., pain in left foot and right hip, "a shuttling back and forth from one side to the other"; at depth of 4 mm., pain in right hip and right side of back, or possibly in both sides of back.

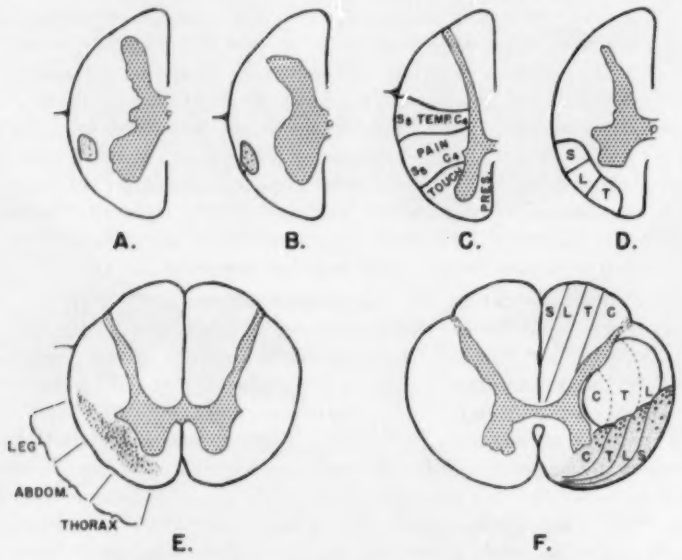

Fig. 4.—Position, extent, and topographic arrangement of spinothalamic tract, as depicted by (*A*) Gray,[16] (*B*) Ranson,[17] (*C*) Foerster,[18] (*D*) Riley,[19] (*E*) Hyndman and Van Epps,[10] and (*F*) Walker.[9]

The topographical distribution of the secondary pain-conducting fibers within the anterolateral column is a point of great practical interest. Evidence from electrical stimulation within this area confirms the common experience of surgeons (Hyndman and Van Epps [10]; Walker [9]) that the progressive decussation of spinothalamic axons at ascending levels tends to displace the more caudal fibers to a more dorsal and more lateral position. The most recently crossed will therefore occupy the most ventral and medial position (Fig. 4). Advantage can be taken of this fact to secure a limited brachiothoracic analgesia, as produced by Hyndman and Van Epps.[10] In the case of the woman illustrated in Figure 5, the incision at C2, which was begun at a point 1 mm. ventral to the dentate ligament, was carried to a depth of 6 mm. and emerged well in front of ventral spinal root. Such limited analgesia, however, is not

certain to persist. In this case of striking early success, in which pain from supraclavicular breast metastases was so specifically interrupted, reports six months later indicated some return of pain.

Axons conveying pain from the lower sacral dermatomes are concentrated in the lateral region just in front of the dentate ligament, as clearly demonstrated by Kahn and Rand [20] and Nulsen and Grant.‡ Their patients, in whom the most dorsolateral sector of the anterior quadrant was spared at the first incision, complained of pain in the perineum and buttocks at testing on the operating table, but lost this residual area of sensation when the cut was extended dorsally to the plane of the dentate ligament, or a little behind this plane.

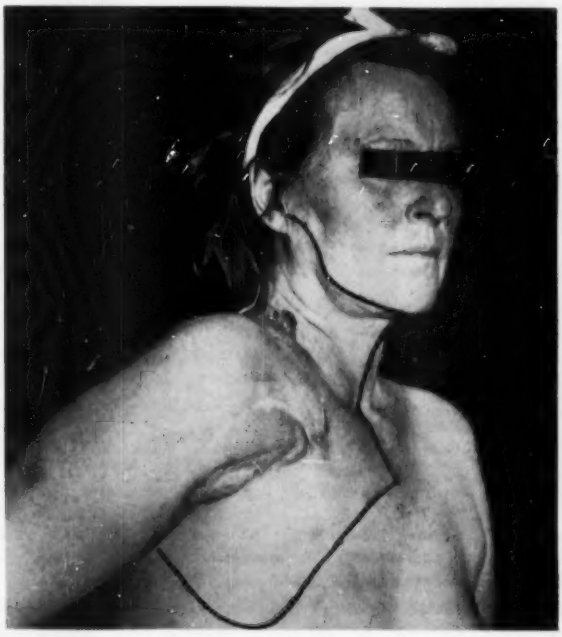

Fig. 5.—Selective chordotomy at C2.

This woman, G. F., had recurrent carcinoma of the breast invading the brachial plexus and producing pain in the shoulder and arm. The incision was made 1 mm. anterior to the dentate ligament and carried to a depth of 5 mm., and then well forward and medial to the plane of emerging anterior roots.

Other postoperative observations indicated that islands of hypalgesia with recurrent pain may open up in ways that are not altogether compatible with the simple topographical arrangement described above (Fig. 6).

Patient Max K. (MGH U-772280), a farmer who had suffered painful injuries to his knee when tossed by a cow, had a chordotomy performed, with complete analgesia to the umbilicus. In spite of this he soon began again to complain of pain on movement of the knee. After the passage of six months it was obvious that a large area of skin in his lower thigh and leg was

‡ Nulsen, F., and Grant, F. C.: Report to Society of Neurological Surgeons, Philadelphia, 1952.

only hypalgesic, although analgesia remained complete in the left lower abdomen, groin, perineum, and buttock. At present, a year after the operation, analgesia has disappeared entirely and a 2-gm. pin causes disagreeable tingling sensation, although he still cannot discriminate between heat and cold.

An identical situation arose in the case of Joseph H. (MGH U-767767), who had been subjected to a chordotomy at C2 for postoperative intercostal neuralgia following transthoracic repair of an hiatus hernia. Here analgesia remained complete from the shoulder down to the sacral region save for the gradual appearance of islands of hypalgesia in the lower thorax. His recurrent pain was relieved by cutting the 7th to the 11th thoracic posterior spinal roots.

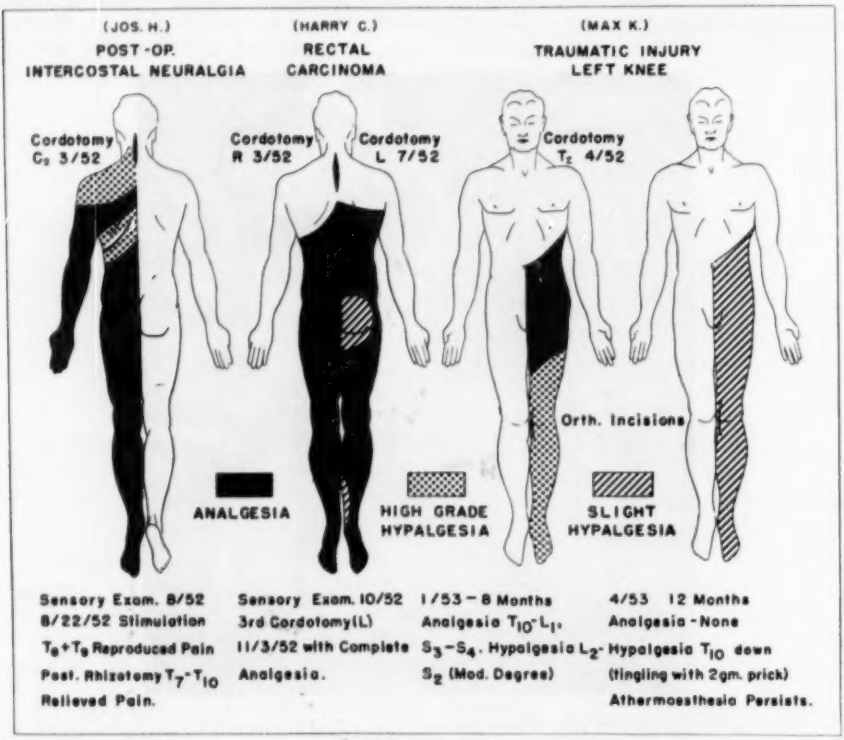

Figure 6

A final instructive case is that of Harry C. (MGH U-756313). This man, who had recurrent carcinoma of the rectum, had had previous bilateral anterolateral chordotomy in the preceding year, with analgesia to the umbilicus. Pain had recurred in the perineum and buttock on the right side, where pinpricks could be detected as having a sharp quality, despite full analgesia in the higher sacral, the lumbar, and the lower thoracic dermatomes. In repeating the section of the left anterolateral quadrant sacral analgesia could not be obtained by cutting more dorsally at the level of the dentate ligament, as I had expected, but appeared as the incision was carried through the ventromedial fibers. Analgesia was then complete from the nipple down, and his pain was relieved. This is evidence for aberrant sacral axons in the ventromedial portion of the cord.

As a general rule the return of sensation in the uppermost dermatomes can be logically attributed to incomplete transection of the most medioventral fibers, and in

sacral areas, to the sparing of fibers in the plane of the dentate ligament. It is impossible to account for fading analgesia in intermediate zones except by the presence of aberrant fibers. This is, fortunately, a rare situation.

These observations, based on purposefully or accidentally incomplete transections of the anterolateral columns of the human spinal cord, or the electrical stimulation of discrete areas, show that there may be wide variations in the distribution of the pain fibers, as well as in the number of spinal segments required for their decussation. To attain consistently satisfactory results from chordotomy, the incision into the anterior quadrant must be an extensive one, and it must be made a generous number of segments above the level desired for permanent analgesia. Furthermore, this level must be verified on the operating table, as the surgeon will often find that his first incision is inadequate and must be increased by a second, or even a third, deeper and more ventral cut.

Massive ventromedial incisions, such as we are advocating, which include virtually the entire anterior quadrant, were illustrated long ago by Foerster and Gagel.[15] Provided due respect is paid to the anterior spinal artery, this causes no further complications than the more parsimonious, less effective incisions so often advocated (Davis [6]).§ White, Sweet, Hawkins, and Nilges [2] pointed out that deleterious sensory changes, other than thermal loss, are minimal. When one stops to consider that the sensibility to touch by graded von Frey hairs may remain unchanged, one wonders whether the ventral spinothalamic tract is really an important pathway of tactile impulses, as described by Ranson and Clark.[5] Lack of any noticeable lower extremity weakness in the patient whose spinal cord is illustrated in Figure 3*A* indicates that injury to the ventral, or direct, pyramidal tract need not concern the surgeon. The complications following anterolateral chordotomy are related to fiber tracts in contact with its dorsal boundary—viz., the pyramidal tract in the lateral column, the sympathetic fibers || that lie at its ventral margin, and the sensory pathway from the bladder, which lies in association with other sacral pain axons in the dorsolateral portion of the spinothalamic complex (Nathan and Smith [22]). The relatively rare incidence of serious injury to these fibers has been discussed in a separate report with Sweet, Hawkins, and Nilges.[2] Experience has taught us, and also Nulsen and Grant,¶ that even when the incision involves the most ventral portion of the pyramidal tract a millimeter or so behind the dentate plane, there will be no lasting weakness on the side of the incision (Fig. 3). This fits in with the experience of Putnam [23] and Ebin,[24] who have deliberately severed a large portion of the lateral quadrant in their attempts to relieve Parkinsonian tremor but have seldom produced striking paralysis. On the rare occasions when serious weakness has followed anterolateral chordotomy, I believe it has been caused by injury to one of the segmental branches from the anterior spinal artery which supply the lateral column (Suh and Alexander [25]) or through the neglect of the surgeon to define the exact point of attachment of the dentate ligament.

§ Davis,[6] p. 453, states: "An incision which begins at the level of the dentate ligament, anterior to its insertion, and finishes in the anterior spinal nerve rootlets, and is a minimum of 3 mm. in depth, will section the fibres in the lateral spinothalamic tract."

|| Evidence for this position of the sympathetic axons is the frequent appearance of Horner's sign, together with warming and drying of the ipsilateral extremities, after high cervical chordotomies, as well as the fall in blood pressure that we have often encountered after bilateral tractotomy, which is occasionally an annoying complication.[21]

¶ Personal communication to the author, 1953.

Ranson and Clark [5] state that when the spinothalamic tract is cut on only one side, the analgesia produced on the opposite side of the body "involves the skin, muscles, fasciae, tendons, and bones but not the viscera. Bilateral section is required to abolish visceral pain." This misconception probably arose from observations made on animals. The failure of staggered hemisections on both sides of the cord to relieve biliary pain in dogs has been emphasized by Davis, Hart, and Crain.[26]

Such evidence derived from experiments on the nervous system in animals has often proved misleading when applied to man. Clinical observations, listed in Table 1, suffice to disprove the hypothesis that one-sided pain from a viscus travels upward in both anterolateral columns to a clinically significant extent. Seven patients with satisfactory unilateral analgesia were tested by retrograde ureteral catheterization and distension of the renal pelves by Dr. Walter S. Kerr. Injection on the control side of 8 cc. or more of fluid invariably produced pain, and usually nausea, while a volume of 15 cc. was easily tolerated on the side of the analgesia. In five of these subjects no sensation of pain was noticed, while in two others mild discomfort without nausea was experienced after injection of 30% more fluid than could be tolerated on the

TABLE 1.—*Visceral Sensation After Unilatera. Chordotomy*

Distension	Sensation of Pain	No. of Cases
Distension of renal pelvis	No pain	5
	Reduced pain	2*
Distension of duodenum by insufflation of balloon on analgesic side	No pain referred to analgesic or to normal side	7
	Reduced pain referred only to normal side	5
Distension of small intestine by carcinoma after rt. chordotomy	No pain on L side (analgesic to T7); severe on R	1

* On control side 30% less fluid induced pain and nausea.

normal side. Distension of intestinal loops at different levels on the analgesic side with balloons inserted under fluoroscopic control by Dr. William P. Chapman produced no discomfort in seven subjects, while five others reported that milder pain was referred across the midline to the normal side. Similar evidence was obtained from a recent patient (Calixte L., MGH U-780681 BM), on whom a right anterolateral chordotomy had been performed, with a level of analgesia at T8, for recurrent carcinoma of the rectum because of intolerable bouts of pain in his left lower abdomen and leg. Several months later he developed acute intestinal obstruction from adhesive constriction of a loop of ileum in the pelvis. He reentered the hospital with vomiting and great distension but said he could feel the bursting pain only on his right side. We have also had a patient under observation in whom left-sided anterolateral chordotomy gave complete relief from chronic persistent pain after multiple operations on the biliary tract and pancreas. This operation was performed 11 years previously by Dr. W. J. Mixter, before we appreciated the effectiveness of sympathectomy in the relief of pain of purely visceral origin.

A few varieties of pain, however, can still be felt in areas where cutaneous analgesia appears to be complete. Examples are seen in the following cases, in all of which the patients continued to complain of severe discomfort after apparently satisfactory transections of the anterolateral column.

1. Muscle cramps and spasm: We have seen this in two cases of spinal arachnoiditis, and in two other cases in which they were secondary to cord injury and combined system disease associated with diabetes mellitus.

2. Injuries of the spinal cord proper (in contrast to those of the cauda equina, which respond well to chordotomy): The patient generally fails to derive any relief from radicular pain referred to the abdomen and legs. We have encountered three such failures at the Massachusetts General Hospital and the Veterans Administration Hospital, Framingham, Mass.

3. Burning pain in the rectum and perineum: Failure to relieve this type of discomfort occurred after bilateral chordotomy in one case of carcinoma of the ovary and after unilateral sections in two cases of adhesive arachnoiditis of the cauda equina. In the latter pain referred to the leg was relieved despite persistence of the sacral burning sensation.

4. Painful postural sensations in a phantom limb: In 14 such cases reported by White and Sweet [27] pain persisted in one upper and another lower extremity despite high levels of apparently complete analgesia. The word "apparently" is used advisedly, because it is manifestly impossible to test the amputated part for sensory spacing. Fading of analgesia, illustrated in Figure 6, in the case of Max K. cited above would not have been detectable if his leg had been amputated in the upper thigh.

What is the explanation for these failures? Does the residual pain actually come from the periphery? Or, in the case of distorted postural sensations in an absent limb, is it a projection from the highest level of cortical integration, which so interested Hughlings Jackson and also Riddoch? [28] Can pain be transmitted over the lateral or posterior columns of the spinal cord? A recent article has suggested the presence of afferent fibers in the pyramidal tract, but Brodal and Walberg [29] believe that centripetal conduction in these axons is related to the Babinski response, and not to conscious pain. On electrical stimulation of the corticospinal pathway in the conscious patient we have evoked pain in the ipsilateral leg, but this may have been carried over the more superficial axons of the direct spinocerebellar tract. The posterior columns are so sensitive that pain responses are evoked with a 0.1-volt stimulus, or even on the mere contact of the electrode. Sensation is felt in various areas on the corresponding side of the body and also on the contralateral side as the midline is approached. When procaine is applied to the pia, these responses persist on deep electrical stimulation. Browder and Gallagher [30] and Pool [31] claimed that the disagreeable postural illusions of the phantom limb can be relieved by cutting the tract of Goll or Burdach. My single resort to this procedure proved fruitless, and Pool has written me that he no longer considers it a useful operation, but Browder states that this is still his operation of choice.

By process of exclusion many, if not all, of the residual painful sensations that enter the sensorium from areas rendered analgesic by chordotomy must reach the thalamus in the posterior columns. It is easy to believe that this is the afferent pathway in painful spasms of skeletal muscle, as muscle stretch and proprioceptive impulses follow this route. Nathan and Smith [22] have also shown that stretching of the perineal and periurethral tissues in the passage of urine sends impulses over this route, which enable the bilaterally chordotomized person to realize when he is passing urine. Stretching of the bladder wall must also initiate impulses over this route, as we have found that in the course of bladder and rectal filling postchordotomy discomfort

is manifested at levels of pressure that induce active stretch contractions. Kuru and his associates [32] have recently succeeded in recording spike potentials from the superficial central portion of the posterior funiculus on filling the bladder. Furthermore, the observations of Sarnoff, Arrowood, and Chapman [33] with differential spinal anesthesia have likewise indicated that the sensation of rectal filling ascends in the posterior columns. Under these circumstances the dilute procaine solution blocks the finely myelinated and unmyelinated fibers in the posterior roots that contribute to the spinothalamic tract, but does not interrupt the larger myelinated sensory fibers that send their central axons rostrally in the posterior columns.

TABLE 2.—*Types of Stimulus Often Causing Pain in "Analgesic" Zones* *

	Pain on Stimulus Absent	Pain on Stimulus Reduced as Compared with Normal Side
Achilles tendon pressure	6	6
Testicular compression	2	8
Pressure on bone (50 lb./sq. in.)	9	7
Hair pulling	17	3
Bipolar electrical cutaneous stimulation (40-140 volts)	..	20
Trauma		
Fractured ankle	..	1
Contusions to thigh	..	1

* From article by White, Sweet, Hawkins, and Nilges.[2]

TABLE 3.—*Effect of Anterolateral Chordotomy on Pain in 210 Patients*

	No. Operations	Per Cent
Early results following 241 operations (up to 1 mo. postoperatively)*		
Analgesia and complete relief of original pain	196	81
Partial return of pain (insufficient to require narcotics)	23	10
Failure to relieve pain on contralateral side	22	9
Late results of unilateral chordotomy in 20 patients subjected to detailed follow-up studies (5 mo. to 10 yr. after operation at T2 or T3)*		
Effective relief, or no medication required (average 46 mo.)	15	75
Partial relief (average 40 mo.)	2	10
Failure (average 63 mo.)	3	15

* Cases previously reported by White, Sweet, Hawkins, and Nilges.[2]

Unpleasant sensations that may persist in the presence of analgesia are listed in Table 2. It may be also noted in passing that the sense of ticklishness is often preserved, although itching, being a form of pain, is lost.

Although this lecture in not directly concerned with the clinical problems of chordotomy, it is important in concluding the section on pain transmission within the spinal cord to state just how effectively desired levels of analgesia can be attained and maintained. This is the best way of making sure that the more fundamental anatomical and physiological data I have presented concerning spinal conduction of pain are valid. General statistics of upper thoracic chordotomy are given in Table 3. From these figures one may conclude that a very high proportion of upper thoracic chordotomies, when properly performed and when the pain is localized in the abdomen or lower extremities, will be followed by satisfactory analgesia. Of the group evaluated at discharge from the hospital 19% had failed to derive effective relief. In 9% of

this group, the cause of residual or recurrent pain was failure to obtain adequate analgesia; in the others, subsequent fading of analgesia to hypalgesia or the spread of malignant disease to higher levels of the body. This occurred chiefly in cases of cancer of the breast and lung. Anterolateral chordotomy proved lastingly effective in only 42% of these. Of 20 cases of chordotomies for pain in nonmalignant conditions, in which prolonged follow-up was possible, in only 15% was severe return of pain complained of on reexamination, at periods averaging over five years. Our results of high thoracic chordotomy in various forms of malignant disease and nonmalignant conditions are further broken down in Tables 4 and 5.

TABLE 4.—*Thoracic Chordotomy in Malignant Disease*

	No. of Cases	Good Relief	Spread to Other Areas	Inadequate Level	Operative Deaths
Breast*	10	3	3	3	1
Lung*	9	5	—	1	3
Gastrointestinal tract	28	24	1	2	1
Urinary tract	9	7	1	—	1
Male genital tract	9	8	1	—	—
Female genital tract	37	27	5	4	—
Bone	15	9	3	1	2
	117	70.9%	12.8%	9.5%	6.8%

* Experience with cancer of the breast and lung has shown that it is particularly difficult to obtain permanent relief in these conditions. This is because of the tendency of such neoplasms to metastasize widely to the cervical nodes and vertebrae, with involvement of the upper cervical spinal nerves and brachial plexus.

TABLE 5.—*Thoracic Chordotomy in Nonmalignant Disease*

	Cases	Good Relief	Failure	Inadequate Level	Operative Death
Stump neuralgia	7	5	2	2	—
Phantom leg	10	8	2	1	—
Paraplegia	7	5	2	2	—
Arachnoiditis	7	5	2	1	—
Tabetic crises	7	6	1	1	—
Postherpetic pain	4	3	1	1	—
	42	76.2%	10	8	0

Table 6 summarizes the early and late results of high cervical chordotomy, in which the anterior quadrant was widely and deeply incised at the junction of the first and second cervical segments by Dr. Sweet and myself. Of this series of 20 patients, we failed to obtain analgesia to the shoulder level in only 2, but the proportion of late failures was discouragingly high (35%). It will be seen that the level of analgesia fell or islands of hypalgesia appeared in 5 of 17 patients within the first six months. Of 11 patients followed over a year, 1 more suffered a drop in level, with partial return of pain, and 1 (the woman whose sensory charts are illustrated in Figure 7) lost her initial complete analgesia over large areas, but, fortunately, not in the region of her pain. In a sufferer from phantom arm pain previously reported on by Sweet,[27] analgesia, which had been present for three years, receded over the distribution of the brachial plexus with return of pain. There was a single operative death, but no lasting impairment of bladder control or weakness of the limbs. The only complication was a disagreeable sense of paresthesia in the hypalgesic leg of Patient Helen M.

The replacement of analgesia by hypalgesia in the lumbosacral dermatomes can be accounted for by failure of the surgeon to include the most dorsolateral fibers of the spinothalamic tract. I am beginning to suspect that in high cervical chordotomy it is necessary to carry the incision somewhat dorsal to the plane of the dentate liga-

TABLE 6.—*Results of Anterolateral Chordotomy at C2*

Patient	Diagnosis	Analgesia to Shoulder Level					Comment
		Postop.	6 Mo.	1 Yr.	2 Yr.	4 Yr.	
Margaret M.	Shoulder amputation with phantom arm	+	0	..	..	..	Pain returned as level fell
Robert S.	Forearm amputation with phantom hand	+	+	..	..	..	Analgesia to C8 without benefit
James W.	Midhumeral amputation with phantom hand	+	+	+	+	..	Effective relief
Mary H.	Post-traumatic neuralgia of arm	+	0	..	..	..	Pain returned as analgesia disappeared
Helen M.	Median nerve injury with overresponse	0	..	..	..	..	Unable to obtain analgesia in two separate operations; disagreeable paresthesia in hypalgesic leg
Christine H.	Postoperative neuralgia (T1-T3)	+	+	+	0	..	Effective relief; hypalgesia in arms and lower body after 1 yr., but analgesia remains in critical upper thoracic dermatomes
Grace F.	Carcinoma breast with supraclavicular metastases	+	0	..	..	..	Analgesia limited to C3-T3 faded
Mahmed L.	Carcinoma, apex of lung	+	+	+	..	..	Effective relief
Frances C.	Thoracic neuralgia of unknown origin	+	+	+	..	..	Effective relief
Vena O.	Postherpetic neuralgia (T7)	+	+	+	+	..	Effective relief
Joseph H.	Intercostal neuralgia post-thoracotomy	+	0	..	..	..	Analgesia faded at level of pain (T8-T10)
Eileen E.	Intercostal neuralgia post-thoracotomy	+	+	+	..	..	Effective relief
Herbert L.	Cauda equina injury with leg and abdominal pain	+	+	0	..	..	Hypalgesia C5; analgesia T10 with recurrent pain
Helen C.	Thalamic pain	+	+	+	..	..	No relief despite analgesia to chin
Simpson B.	Postherpetic neuralgia (upper thoracic)	+	+	+	+	+	Effective relief at 7 yr.
Ruth L.	Carcinoma breast with radiation of pain to arm	+	+	+	*	..	Effective relief for 14 mo.
Fred. S.	Tabetic crises	+	+	+	+	+	Effective relief
Rose R.	Carcinoma breast with arm radiation	..	..	..	..	..	Operative death
Julia R.	Carcinoma breast with arm radiation	+	0	..	..	..	Analgesia faded in 2 wk.
Harry T.	Dysaesthesia from thoracic chordotomy	0	..	..	..	..	Unable to obtain high analgesia or reduce discomfort
							Totals
	Postoperative death	1	..	..	..	..	..
	No. of patients followed	19	17	10	5	2	..
	Analgesia with effective relief	15	12	10	4	2	..
	Apparent analgesia without relief	2	..	..	..	..	2
	Analgesia not obtained	2	..	..	..	..	2
	Fall in level with recurrent pain	..	5	1	..	..	6
	Fall in level without recurrent pain	..	..	..	1	..	1

* Upper cervical metastases produced recurrent pain at 14 months; no opportunity to repeat sensory examination.

ment if one wishes to make certain that analgesia will persist in the lower thoracic and lumbosacral dermatomes. This opinion has been reached independently by Nulsen and Grant,‖ and we have seen no striking evidence of leg weakness when the incision is carried into the most ventral portion of the pyramidal tract (see above).

One can explain an early change from analgesia to hypalgesia by the assumption that a proportion of the pain fibers have been contused, rather than severed, by the chordotomy knife. It is not uncommon to see the upper level of analgesia drop several

‖ Personal communication to the author, 1953.

segments during the first week. Allowance for this should be made by the surgeon, even though there will often be little change. It is the late extensive fading of analgesia, months, or even years, after the incision, that will plague even the best operator, and which he is powerless to prevent, especially when the operation is done for pain in the arm or upper chest. Further knowledge of the position of the pain fibers is needed before high cervical chordotomy can be regarded as a satisfactory operation.

PAIN TRANSMISSION IN VISCERAL NERVES

When Hughlings Jackson suggested the study of conduction of "particular impressions" by nerve tissue rather than the morphology of the neurones, he was interested in higher levels of the central nervous system. Even the pioneers who

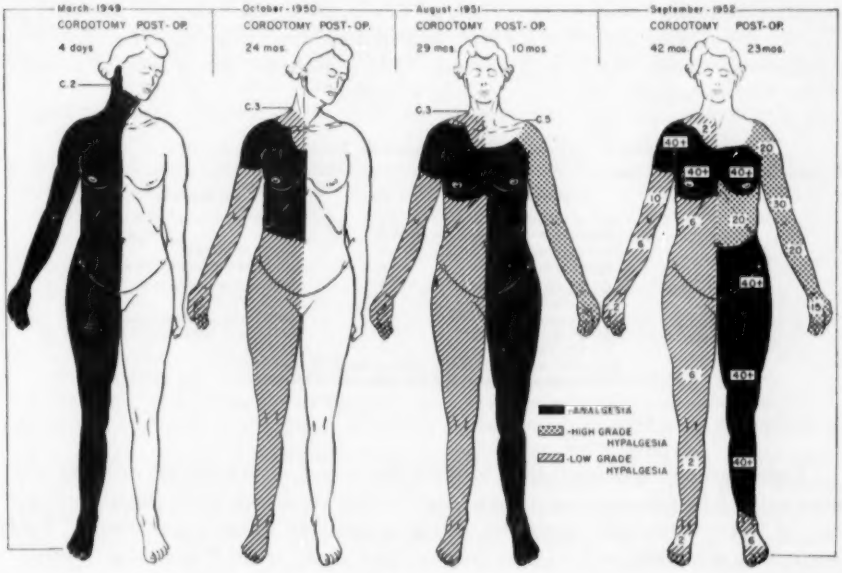

Figure 7

studied visceral innervation—Claude Bernhard; Gaskell and Langley, who were working during his lifetime; Cannon, who came a generation later, and the Swedish surgeon Lennander,[34] who first became interested in visceral sensation when he began to operate with use of local anesthesia— were quite unaware that visceral, like somatic nerves, play a direct role in the transmission of pain. Their action in this respect could not be elucidated by the method suggested by Jackson until natural physiological stimuli were discovered which could arouse pain: distention, in the case of hollow viscera (Hurst[35]), and anoxia, in the case of muscular organs like the heart (Sutton and Lueth[36]).

Lennander was misled into thinking that the viscera were insensitive because of their paucity of sensory nerve endings (Carpenter[37]; Feindel, Weddell, and Sinclair[38]). Under these circumstances, the sensory threshold is high, and it requires spatial summation from a massive stimulus to activate a sufficient number of nerve

endings in order to evoke a conscious response.* For this reason nothing is felt on cutting or burning a loop of intestine or pricking the epicardium, while intestinal distention or myocardial ischemia gives rise to severe pain.

The experiments of Lewis [40] have shown that there is no fundamental difference between pain responses of viscera and other deep structures, such as skeletal muscle. The reason is obvious from the work of the Oxford school of anatomy (Weddell [41]; Le Gros Clark [42]; Weddell, Sinclair, and Feindel [43]). These investigators showed that localization of pain depends on the density of the plexus of undifferentiated nerve endings subserving pain. This is well developed throughout the surface of the body and the naso-oropharyngeal mucosa, and also in many parts of the peritoneum, where stimuli are localized with accuracy. In the viscera, as in striated muscle, sensory endings are sparse, and there is an absence of overlapping of fibers, which makes accurate localization impossible. Thus, as Lewis stated, the difference in ability to localize pain on the surface of the body and in deep structures, including viscera, is a quantitative rather than a qualitative one. I have discussed this in detail in a recent Osler Society lecture at the University of Vermont.[44]

TABLE 7.—*Stimulation of Splanchnic Nerves and Ganglia*

	Stimulation	Volts	Pain Reference
Mava S.	Minor splanchnic	0.2	Right upper quadrant
	Least splanchnic	10.0	None
Eva S.	T12 ganglion	2.0	Right abdomen
	Minor splanchnic	2.0	Right lower quadrant
Elwood C.	Major splanchnic	1.5	Right upper quadrant
	T11 ganglion	0.6	Back and side
Harry T.	Major splanchnic	5.0	Left lower quadrant, chest*
	Minor splanchnic	5.0	Left lower back, umbilicus
	T11 ganglion	5.0	Umbilicus

Stimulation of peripheral stump never evoked pain.
White and gray rami seem to transmit pain equally.

* Stimulation above T10.

Unfortunately, it is impossible to study the course of visceral nerve fibers that conduct pain by degeneration studies because these are largely unmyelinated. Much can be learned, however, from stimulating sympathetic ganglia and trunks. Past attempts in this direction have been few. Adson [45] and Leriche [46] were able to stimulate the major splanchnic nerve in the course of operations under spinal anesthesia. Under these conditions pain was felt, but beneath the scapula or deep in the chest in the region of the heart. These experiments were not physiological because only the uppermost splanchnic rami, whose fibers enter the spinal cord over the fifth and sixth thoracic posterior roots, were able to conduct. The more important lower posterior rootlets down to T9 must have been blocked by the spinal anesthetic. When we have stimulated the central cut end of the major and minor splanchnic nerves just above the diaphragm in the course of thoracolumbar sympathectomy under local anesthesia (preliminary nitrous oxide and thiopental having been used during the exposure and the patient then allowed to wake up), pain has been clearly felt in the abdomen or back on the side of stimulation. This was described as a deep, diffuse, poorly localized sensation in each of four patients tested (Table 7). On stimulation of the left major splanchnic above its connecting ramus with the ninth thoracic ganglion, pain was felt

* An analogous situation may be reproduced in the sensibility of the skin following certain types of lesions in the parietal lobe (Denny-Brown and associates [39]).

near the apex of the heart. These sensations differed neither in latent period nor in intensity from the well-localized pain evoked by stimulating the 12th thoracic or the 1st lumbar nerve at a similar 0.2- to 5-volt setting of the Grass stimulator. It should be emphasized that this pain is always evoked by stimulation of the central cut end of the splanchnic nerve, and never from the distal stump.

Very similar responses were evoked in seven patients on stimulating lumbar ganglia. Sweet and I have been able to test this in four subjects in the course of resecting the lumbar ganglia (Table 8). When the second lumbar ganglion is stimulated pain is felt widely in the ipsilateral portion of the abdomen and in the lumbar area in the back, with a tendency to center around the umbilicus. On stimulation of L3 pain is felt more in the lower abdominal quadrant and pelvis. In one of these patients who complained of severe stump neuralgia after midthigh amputation, as well as in the other three, it proved impossible to elicit any pain referred to the lower extremity. Simeone,[3] who applied pull-out electrodes to the central stump in three other patients after resecting lower lumbar ganglia, found on electrical stimulation a day or two later that reference of pain was limited to the stimulated side of the abdomen. This signifies that all these structures carry visceral pain fibers which differ neither in their

TABLE 8.—*Stimulation of Lumbar Sympathetic Ganglia*

	Ganglion	Volts	Pain Reference
Ralph T.*	L2	Mechanical	Left upper quadrant
	L3	Mechanical	Pelvis
Elwood C.	L2	1	Loin
T. P.*	L2	..	Left lower quadrant
	L3	..	Loin
Mary K.*	L2	2	Left lower quadrant
	L3	2	Left side and back

* Post-traumatic pain in lower extremity. Leg pain not reproduced by sympathetic stimulation.

threshold nor in their latent period from the neighboring spinal nerves. On the basis of histological evidence it has long been known (Kuntz [47]) that the major splanchnic trunks carry many large well-myelinated axons corresponding to the rapidly conducting pain fibers which supply the surface of the body. Sheehan [48] has shown that when the splanchnic nerves are cut, the Pacinian sensory corpuscles in the mesentery degenerate, but it is impossible to follow degeneration of the fine unmyelinated C fibers by any microscopic technique. While direct stimulation experiments in man have shown so clearly the role of the sympathetic nerves in the conduction of visceral pain, they have afforded no evidence to suggest that the sympathetic can act as an afferent pathway for pain from the lower extremities.

In our stimulations of the upper thoracic ganglia, pain has been evoked in the precordium, deep in the chest and back, and for variable distances down the upper extremity (Table 9). These responses resemble the pain in angina pectoris and aneurysm of the aortic arch. In contrast to the lack of leg radiation when the lumbar ganglia were stimulated, there was distinct reference of pain down the length of the arm and into the entire hand in two of six patients so far tested. In patient Hazel W., MGH U-206848, a woman with a causalgic syndrome who has now been relieved for two and a quarter years by her sympathectomy, stimulation of the third thoracic ganglion reproduced her characteristic burning pain in the shoulder, arm, and hand. This fits in with an observation of Walker and Nulsen,[49] who carried out similar stimulation experiments in the course of a number of wartime sympathectomies and reported that

radiation to the arm occurred only in cases of causalgia. Patient Ethel L., MGH U-756888BM, with Raynaud's disease, recently operated upon by Dr. William H. Sweet, has shown us that arm radiation can take place on stimulation of either the white or the gray communicant rami of the first thoracic ganglion. This gave rise to a pricking sensation throughout the hand on the application of a 2- to 4-volt stimulus to either of the intact rami, or to their cut ends, attached to the first thoracic nerve. The possibility that current spread to the spinal nerve was ruled out by the fact that its direct stimulation gave rise to a very different response.

In the past there have been two schools of thought on the role of the sympathetic innervation in painful syndromes of the extremities which respond to sympathectomy. Foerster,[48] Slaughter,[50] Kuntz and Saccomanno [51] and Threadgill [52] have presented clinical and experimental evidence from animals that the sympathetic may be an accessory system for the conduction of pain. The most convincing evidence for this hypothesis is the case reported by Echlin.[53] In his patient with phantom pain following lower extremity amputation, the disagreeable sensations were reproduced on central

TABLE 9.—*Stimulation of Upper Thoracic Sympathetic Ganglia*

	Diagnosis	Ganglia	Volts	Pain Reference
Eva S.	Hypertension	T1 and T2	2	Upper arm to elbow
Frederick W.	Post-traumatic neuralgia	T1 and T2	2	Back +; arm 0
Donald T.	Post-traumatic neuralgia	T2 and T3	10	Deep under scapula
Hazel W.	Post-traumatic neuralgia	T2	10	Precordium
		T3	14	Burning pain in shoulder, arm, and hand
Frederick D.	Post-traumatic neuralgia	Stellate	..	Upper arm, ulnar neuroma
Ethel L.	Raynaud's disease	T1	14	None
		T2	14	None
		T1 lateral ramus communicans*	2	Prickling throughout hand
		T1 medial ramus communicans*	4	Prickling throughout hand

* Pain evoked only on stimulation of cut end of ramus connected with first thoracic nerve.

stimulation of the lumbar ganglia and, according to a recent letter, have been relieved for several years following ganglionectomy. Ellonen [54] has also reported some instances of relief following sympathectomy, but his follow-up study was inadequate, and Kallio [55] stated that pain in these patients has usually recurred. At the Massachusetts General Hospital neither sympathetic block nor resection has ever been known to relieve phantom sensation or any sort of pain following arm or leg amputation, and we have seen these complications develop when amputation has been performed after preliminary sympathectomy.

In opposition to the theory that sympathetic axons may constitute an accessory pathway for pain from the arm or leg, Doupe, Cullen, and Chance,[56] as well as White, Heroy, and Goodman,[57] have favored the theory that relief of causalgia and certain other post-traumatic neuralgias by sympathectomy is due to interruption of the efferent limb of a reflex arc whose afferent component is in the sensory fibers of the peripheral nerves. This is based on the experiments of Granit, Leksell, and Skoglund,[58] which showed that motor root discharges may short-circuit to sensory fibers at a point of injury in the peripheral nerve. The fact that tetraethylammonium compounds, which block sympathetic synapses but not conduction, offer relief of causalgic pain (Conley and associates [59]) is a further argument in favor of this view. This may also be said of the temporary relief of causalgic pain that follows the chill induced by

intravenous administration of typhoid vaccine (Spurling [60]) or a bout of malaria (Mayfield and Devine [61]), as the period of defervescence is accompanied by a reduction in vasoconstrictor tone.

More data from experimental stimulation in fully conscious intelligent subjects will be required to settle this controversy. Our evidence to date at least shows that the sympathetic innervation cannot be an important accessory pathway for the conduction of pain from the arm, and such a possibility seems even more remote in the case of the lower extremity.

A final point of interest has been the role of the sympathetic communicant rami in conduction of pain. My associate Dr. Sweet has been unable to observe any difference between the so-called white and gray rami in this respect. As Pick and Sheehan [62] have stated, one cannot tell which is which, either by its gross appearance or by its central or more peripheral origin from the spinal nerve. There is likewise no sensory difference on electrical stimulation. Regardless of whether the electrode is applied to the more central or the peripheral ramus, a deep diffuse aching type of pain is usually evoked. After the ramus has been divided, this is felt only when the end attached to the spinal nerve is stimulated.

In summary, we are led to the conclusion that afferent fibers from the posterior root system run in all the visceral sympathetic trunks. As is the case with other deep tissues innervated by somatic sensory fibers, the primary neurons which relay pain from the viscera have synaptic connections with secondary neuron cells in the posterior horn; these, in turn, give rise to axons which cross in the spinal commissure and run upward in the anterolateral quadrant. Whether they are actually incorporated in the spinothalamic tract proper or run as a separate column in a more medial or ventral position matters little. In any case the contralateral component of visceral pain is eliminated after an extensive transection of the anterolateral column, just as completely as painful sensations from skin, fasciae, muscles, ligaments, or bones.

As Ruch [63] has pointed out, there are not enough fibers in the spinothalamic tract to supply all the primary pain fibers that enter the cord via its posterior roots. This means that many pain impulses which reach the posterior spinal horn from a viscus must share a secondary spinothalamic axon with a cutaneous fiber. It is therefore easy to see how sensation from a viscus can be misinterpreted by higher centers as an illusion coming from the surface of the body. Yet interruption of cutaneous inflow will not interrupt visceral pain, as would be implied by Mackenzie's [64] theory of the viscerocutaneous reflex. Clinical observations, summarized in Table 10, show that visceral pain will still be felt despite wide areas of cutaneous anesthesia. Cohen and Jones [68] have twice observed reference of anginal attacks to a phantom arm after amputation at the shoulder. The only way in which peripheral mechanisms that can be eliminated by peripheral denervation appear to play a significant role in the production of visceral pain is in the formation of secondary cutaneous hyperesthesia or muscle spasm (Wolff and Hardy [74]; Sinclair, Weddell, and Feindel [75]).

It is therefore clear that in order to eliminate pain in visceral disease the surgeon must cut the viscerosensory fibers within the peripheral sympathetic trunks, the posterior spinal roots, or the anterolateral quadrant of the cord together with the larger mass of sensory afferent fibers from the surface of the body. The practical value of these observations is shown by the over-all effectiveness of viscerosensory denervation, which has been reported in over 200 cases by White, Smithwick, and Simeone [3] and is summarized in Table 11. As long as a painful condition is confined to a viscus

and has not spread beyond the confines of its capsule by inflammatory or malignant invasion, appropriate denervation can be counted on to bring nearly certain relief, regardless of whether the cutaneous area of reference is denervated or not.

TABLE 10.—*Evidence* * *That Visceral Pain Cannot Be Interrupted by Denervation of Its Cutaneous Area of Reference*

Stimulus	Parietal Anesthesia	Effect on Pain	Reference
Distension of gall bladder in dogs	Intercostal neurectomy distal to origin of rami communicantes †	Unchanged	Davis, Pollock, and Stone [68]
Direct stimulation of nerve at time of phrenicectomy	Cervical plexus block	Unchanged	Woollard, Roberts, and Carmichael [66]
Myocardial ischemia in dogs	Intercostal neurectomy distal to origin of rami communicantes †	Unchanged	White, Garrey, and Atkins [67]
Attack of angina pectoris in man	Procaine injection of precordium Previous shoulder amputation (2 cases)	Unchanged Referred to phantom arm	Lewis [40] Cohen and Jones [65]
Electrical stimulation of duodenum	Local infiltration of abdominal wall	Unchanged	Boyden and Rigler [69]
Distension of ureter	Local infiltration of loin and groin	Unchanged	McLellan and Goodell [70]
Balloon distension of duodenum	Local infiltration of abdominal wall	Pain produced on increasing distension	Wolf, Wolff, and Goodell ‡
Mechanical to duodenal ulcer	Abdominal field block	Unchanged (pain ceased after splanchnic block)	Bentley [71]
Digital compression of inflamed appendix	Abdominal field block	Unchanged	Kinsella [72]
Electrical to cervix uteri	Suprapubic subcutaneous infiltration	Pain on low-voltage stimulation stopped, but always broke through with higher current	Theobald [73]

* With the exception of experimental distension of the gall bladder and the myocardial ischemia carried out in dogs, all these observations were made on human patients.
† Pain no longer evoked after section of corresponding posterior spinal roots.
‡ Unpublished observations cited by Wolff and Hardy.[74]

TABLE 11.—*Neurosurgical Treatment of Pain in Intractable Visceral Disease* *

Condition	Operation	Results			
		Good	Improved	Failure	Death
Angina pectoris	Upper thoracic ganglionectomy	15	..	1†	2
	Posterior rhizotomy	2	..	..	..
	Paravertebral alcohol block	49	16	6†	7
Aortic aneurysm	Paravertebral block with procaine and alcohol	3	..	..	..
	Posterior rhizotomy (T1-T7)	1	..	..	..
Biliary pain after cholecystectomy	Splanchnicectomy	13	..	2	..
Pancreatic calculi	Splanchnicectomy	2	..	1	..
Pancreatic carcinoma	Splanchnicectomy	1	..	1	..
Posterior duodenal ulcer	Paravertebral alcohol block	2	..	..	..
Intestinal dyskinesia	Splanchnicectomy	4	..	1	..
Nephralgia	Splanchnicectomy or denervation of renal pedicle	3	..	..	..
Dysmenorrhea	Presacral neurectomy only	15	3	3	..
	Presacral neurectomy with suspension, etc.	72	4	13	..

* These statistics are a summary of cases reported in detail by White, Smithwick, and Simeone.[3]
† Technical failures from incomplete denervation.

Drs. W. J. Mixter, J. S. Hodgson, H. T. Ballantine, and W. H. Sweet gave me permission to use this material. The data on which this lecture is based are taken from a manuscript of a book on the surgical control of pain which Dr. Sweet and I are writing together. He should therefore be regarded as the co-author of this essay.

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THE INITIAL INTERVIEW

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THE INITIAL, or "diagnostic," interview differs from all subsequent hours spent in psychotherapy. At this first meeting between doctor and patient, many initial impressions are formed on both sides, the beginnings of the relationship are established, and the doctor endeavors to form some tentative diagnostic formulation of the entire problem so that he can plan the most effective course of treatment. Little has been written about this first hour with the patient; this paper represents some of our thoughts on the matter, which we have tried to present in a way that would be helpful to the medical student, intern, and psychiatric resident. We shall discuss some of the theoretical aspects, areas that should be covered, and a few of the practical problems frequently encountered.

One repeatedly sees examples of the difficulties experienced by the neophyte in his attempts in examination of the patient. There is the senior student who spends several hours with a patient conscientiously recording her fears, frustrations, and emotional conflicts. This student, having received the traditional type of outline for "Mental Status Examination," and having duly noted the absence of delusions, hallucinations, obsessions, etc., then sees nothing wrong in recording "Mental content negative." Then there is the resident who becomes so intensely interested in the patient's sibling rivalry that he fails to ascertain the fact that she is unaware of how or when she came to the hospital.

These two examples represent exaggerations of the two schools of thought about the approach to the diagnostic interview. On the one hand, there is the very mechanical, systematic, dehumanized "diagnostic" approach, which attempts to evaluate part-functions of the personality, with total disregard of the fact that these functions are occurring in a complex human being who is at the moment interacting in complex ways with another person, the doctor. On the other hand, there is the completely unstructured, empathic, interpersonal approach, in which the focus of attention is primarily directed toward psychotherapeutic goals, with no attempt at diagnosis per se.

Historically, the "diagnostic" approach grew out of the fact that clinical diagnosis of mental illness was largely in the hands of the state hospital physicians dealing with committed patients. From this, and from the Kraepelinian tradition of thorough descriptive psychiatry, evolved the standardized form for mental status examination still in wide use today This type of procedure is outlined and dis-

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cussed by Preu [1] and Cheney.[2] The obvious limitations of this approach are generally well known. As Menninger [3] has noted, it takes no account of the advance in psychiatry since Kraepelin.

With the advent of more dynamic psychiatry there have been many modifications in our original thinking about the diagnostic examination. As has been noted, the trend has been toward being less "diagnostic" and more "therapeutic" in orientation. This has been a result of our awareness that in psychiatry diagnosis and therapy are inseparably interrelated throughout the course of treatment. With some workers this modern trend has progressed to the point of dispensing with diagnosis. This view is expressed by Coleman: "It is important to introduce patients to treatment immediately, and not first to subject them to any formal diagnostic process. The diagnostic information which is needed can be obtained through the treatment interviews themselves, at least with clinic patients." [4]

One of the earliest and most constructive discussions of the concept of the dynamically oriented diagnostic interview was that of Whitehorn,[5] who pointed out that every interview has psychotherapeutic or psychonoxious influences on the patient. An understanding of the dynamic factors of the patient's problems is of *most* importance, but not to the *exclusion* of the more traditional features of the mental examination, including attention to the evaluation of mental functions. Menninger [3] also places emphasis on these two factors and has presented a very complete outline of the diagnostic interview. The principal objection to such an outline is indeed its extreme thoroughness, since the data called for are so detailed that they would be obtainable only after prolonged psychotherapy.

It is surprising how little attention this subject has received in the literature. Beside the excellent papers of Whitehorn and Menninger, other authors, such as Coleman,[4] Finesinger,[6] and Powdermaker,[7] discuss only aspects of the problem. It is also interesting that only Gelbman and Wake [8] have reported any systematic attempt to learn, even superficially, how the patient feels about one's initial efforts on his behalf. Powdermaker's paper is primarily concerned with common emotional responses of psychiatrists in their first contact with patients and also presents a seminar method of teaching dynamic diagnosis.

Drawing on our own experience and our review of the literature, we have arrived at this viewpoint: While rejecting, of course, the old-fashioned "mental status" inventory, we must also reject suggestions that attempts at "diagnosis" have no place in the first interview. It is our impression that a good diagnostic interview must include some specific evaluation of mental function and attempts at categorical diagnosis, as well as initial efforts at psychotherapy. Of course, the psychiatrist must be sensitive and responsive to the patient's emotional needs, and psychotherapy, in a sense, must begin from the first moment of meeting between doctor and patient. Everything one does with patients must be oriented to meet their treatment needs—not designed to satisfy one's own needs for medical compulsivity for diagnosis or hospital requirements for stereotyped records. However, it is our contention that the first interview should be primarily diagnostic. This means that the doctor's responsibility to the patient can best be fulfilled by obtaining the most complete tentative picture of the patient that is possible. It seems that the initial interviews offer the best opportunity for diagnostic inquiry with the least interference with treatment. Too often, treatment is instituted with inadequate attention to the total picture and significant factors are overlooked—factors that would have

been easily discernible in the initial interviews. So often, for example, intensive uncovering psychotherapy is begun with a patient who, much later, is found to have long been schizophrenic. The patient with impulsive outbursts of anger is treated as a character neurotic but is later found to have considerable memory impairment and to be suffering from organic brain damage. For all its well-known limitations, an effort at diagnostic classification remains one of the useful and necessary tasks in the initial interview.

Actually, methods of examination, like most matters related to psychotherapy, lend themselves poorly to academic summary. The manner of conducting an initial interview should by no means be formal; however, the content of such an interview should be so guided by the physician as to lend it some degree of diagnostic significance. It has been our observation that the use of systematic outlines to guide the beginner has been fraught with many difficulties. Outstanding among these has been the medical student's tendency to codify knowledge so as only to conform to a detailed outline. Generally, then, providing the student with only an outline may seriously restrict his innate capacities for spontaneity and responsiveness. On the other hand, the problem with the new resident is that he usually deplores all outlines, becoming amorphous in his approach to the patient, and is guided largely by a vague but insistent need to "psychotherapeutize." Of course, there really can be no formulae for examination of the patient, any more than there are for the practice of psychotherapy. Outlines such as Menninger's [3] are certainly useful in defining areas for investigation but have little value as a direct guide in conducting the initial interview. The beginning resident finds few discussions of techniques for interviewing a patient; on the one hand, he is told that these are things he can learn only from experience, advice which makes him feel helpless. On the other hand, he may be given an overly detailed outline which he feels he must attempt to answer completely. In either case, he is hampered in his initial efforts at understanding the patient.

However, there are some general principles and specific aids which can be helpful as guides to the beginning resident while he is developing individualized skills, which are best acquired under the guidance of a supervising psychiatrist.

In general, the interview naturally begins with a discussion of what brings the patient to the hospital; the therapist then permits the present illness to unfold, and this usually leads to a discussion of situational factors or of immediate family relationships. Other areas which should receive consideration are those of the patient's past history and early life and, directly or indirectly, some assessing of mental functioning.

From the moment the psychiatrist first sees his new patient, the emotional relationship between the two assumes paramount importance. The doctor's evaluation of the patient begins by observing his responses as they first meet. The manner in which the patient greets the doctor and enters the office may provide valuable clues to some personality characteristics. There is, for example, the very assertive patient who attempts to take command of the situation from the first moment; he may explosively rise from his seat, crush the doctor's hand, and try to place the relationship on a personal basis. Then there is the very shy patient who walks hesitantly down the hall and is reluctant to sit down before being so asked by the doctor. These observations may give important clues as to how both patients handle anxiety-pro-

ducing situations in their interpersonal relationships. Other defense mechanisms may be similarly revealed throughout the course of the interview.

It may be noted here that, oftentimes, certain of these defensive attitudes may arouse negative—or inappropriately positive—feelings in the psychiatrist. At these times it may be somewhat helpful to try to see the patient as a *frightened* and defensive person. Of course, it is seldom possible, in nonanalytic psychotherapy, to really understand one's attitudes toward the patient; but attempts toward this, no matter how superficial, may enhance the therapeutic relationship.

Worth mention in this respect are feelings of insecurity and anxiety experienced by the doctor during periods of silence. Frequently he reacts to this with premature or excessive questioning, reassurance, or explanations, which invariably prevents the patient from relating his story with the proper emphasis. One repeatedly is impressed with the fact that the patient will reveal the most pertinent material after periods of silence. One does, of course, employ judgment in not permitting the patient's anxiety to become excessive.

This principle of allowing the patient a great deal of initiative in relating his story also guides us in our manner of phrasing questions. It is advisable to ask these only in the most general, nondirective way possible. It is only infrequently, and then only later in the interview, that more specific and potentially leading questions need be asked. Often an inquiry which amounts to merely evincing special interest in something the patient has said, or just reflecting on one of his comments, may encourage him to continue his account as spontaneously as he can. When the patient is speaking freely, it is generally unwise to interrupt with questions, even though the topics he refers to obviously require further investigation. These can be returned to later.

In this connection one can keep in mind some of the feelings the patient may have about consulting any doctor, particularly a psychiatrist. First of all, on a conscious, rational level, he comes because he is aware of symptoms, illnesses, or problems, which he hopes the doctor, as society's expert in this field, may be able to alleviate or "cure." Also—still on a conscious level—he has many more or less rational fears of new dangers which may beset him as a result of the doctor's findings. Will the doctor tell him that he has a serious illness? Must he have a dangerous operation? Will he have to go to a hospital? Then, if there is a question of his having an emotional or mental illness and if the doctor is a psychiatrist, his fears will be even greater. Will the doctor think he is "insane"? What will people think of him for seeing a psychiatrist? Even aside from the very real social stigma, which should not be present, but unfortunately often is, everyone tends to be frightened by the idea of having to see a psychiatrist. This deep fear is related to one's sensing, somewhat correctly, that having an emotional illness implies losing some degree of socially acceptable control over one's feelings. This fact is an important one, and one that is often overlooked, even by psychiatrists. The beginning psychiatrist will do well to keep it in mind, and to attempt to respect his patient's fears about psychiatry.

In addition to these relatively conscious wishes and fears the patient experiences with the doctor, there will be many unconsciously determined attitudes. These may, of course, be quite out of keeping with the actual patient-doctor situation. The possibilities here are, of course, innumerable; but, briefly, patients may see the doctor as someone awesome, punishing, omnipotent, loving, all-giving, or seductive—just as they, as children, once viewed their parents or other important figures.

Thus, because of both conscious and unconscious attitudes, the patient will have strongly mixed feelings about confidence in the doctor. It is important to *permit* him to tell as much as he can. This must inevitably entail some anxiety on his part. Attempting to relieve the patient's anxiety—and one's own—by premature reassurances, or explanations, will always tend to prevent the patient from revealing more about the underlying problems.

One may hear the objection that such relatively inactive approach on the doctor's part may be effective only in situations where there is ample time. What about the common clinic situation in which it may be necessary to reach some tentative diagnostic evaluation after one brief interview? Is it not here necessary to question the patient quite actively, in order to get more information faster? Actually, even here we find that helping the patient to tell his story is not only the most reliable, but also the quickest, way to get some understanding of him and his illness. It is always possible to ask a few clarifying questions at the end without attempting to "push" him throughout the interveiw.

As has been mentioned, most iaterviews begin with, or quickly come to, a discussion of the patient's presenting complaint. There are occasional instances in which one senses that the patient is extremely fearful, and that it is best to discuss briefly some relatively neutral subject with him until he seems more at ease. However, usually, after introductions are completed and the patient has been made comfortable in the doctor's office, one asks about his problems. This may be done by saying, "Tell me about your difficulties," or "Will you tell me what brought you here?" The patient then describes in his own words his conception of his problem and how it affects him. This by itself often gives a clue to the patient's motivation for treatment; for example, the patient may say, "Oh, I came because my mother (or the judge, or the wife) insisted upon it." From here he usually launches into an account of the so-called "present illness." However, he may, for example, first discuss family relationships. In either case one can learn most by attentively listening, rather than by feeling obliged to follow an arbitrary schedule of sequence of events in the interview.

When he does come to describe the present illness, he is permitted to do this spontaneously; however, the psychiatrist should later make such inquiries as are necessary to elicit details concerning its inception, possible precipitating factors, chronologic progression, interrelationship to other events, any previous efforts to alleviate the illness (including psychiatric treatment), and circumstances leading to this consultation.

The patient's story of his illness will include not only symptoms, but various references to other persons and historical events in his life. This gives important background information. Futhermore, it provides a good basis, within the framework of the patient-physician relationship, to inquire quite naturally into almost any area of the patient's life. Thus, it is rarely necessary suddenly to introduce an entirely new topic, for the patient usually may be guided into discussing any subject by reference to some previous remark.

One area that is frequently neglected is that having to do with information concerning the patient's immediate life situation, with all its ramifications into the community, economic, and occupational spheres. These important factors have often been overlooked because of modern preoccupation with the significance of childhood conflicts in forming the bases for adult neuroses. Actually, information

about the current or recent life situations is vital in obtaining a clear picture of the entire problem. The manner in which the patient is functioning in family and community may give valuable clues to ego strengths and defense mechanisms. The understanding of certain current circumstances and recent events in the patient's life may lead us to alter our opinion of the significance of attitudes or fears he had previously described. For example, a man whose son has just been hospitalized for poliomyelitis would be expected to show anxiety in the face of this very realistic threat. An evaluation of the patient's available resources and limitations—economic and social, as well as personal—is essential to any consideration of a rational treatment plan for him.

Actually, any adequate understanding of the patient must take into account both his current situation and his previous life experiences. Thus, some broad survey of his "past history" is essential even to the most tentative initial evaluation. This survey should include some data relative to parents, early development, family relationships, school and social adjustment, psychosexual development, occupational history and marital adjustment, relationships to children, etc.—with particular reference to habitual modes of reacting to stress in any of these areas.

The appraisal of certain mental functions, which we feel is necessary in the initial evaluation, may be accomplished in various ways. As is the case with other aspects of the patient's personality, these functions are usually best evaluated in an indirect manner, with the observation later supplemented by more direct questions, if necessary. If one spends a period of time carefully observing a patient and listening to him talk, it is usually possible to get some evaluation of his orientation, his memory, his judgement, his intelligence, and his thought processes. The examiner is usually able tentatively to conclude that these functions are intact, unless the patient has said something to shed reasonable doubt on, say, his memory functioning. This may have come in the form of a subjective complaint of memory difficulty, or the examiner may have noted confusion as the patient endeavored to recall past events. In either case the physician now has a basis for inquiring further into the area of memory functioning, quite naturally and quite within the framework of the developing relationship between patient and doctor. When such a doubt about memory functioning arises, it is usually best to make a mental note of this and then, later in the interview, to ask about difficulties with memory and, perhaps, to give specific memory tests.

In a similar way—at first indirectly, and then, later, more directly—the other part-functions of the personality can be assessed. For example, a disorder in the logical progression of thought is often best revealed by the patient's spontaneous associations as he talks, although falsely positive leads may often present themselves here. Impairment of abstract thinking may be indicated by the unusual literality of the patient's conclusions, or by his reports, or demonstrations, of gross social tactlessness. Again, the use of specific tests, such as those involving the interpretation of proverbs, may be considered.

There are those who advocate the extensive use of these testing procedures in evaluating specific mental functions. This approach is indeed tempting, particularly to the beginner, because it seems to offer a source of quick, objective data. Actually, we feel that while simple tests for memory, abstract thinking, and the like, are diagnostically useful in certain situations, their value is usually distinctly limited. Their use introduces an atmosphere of interrogation which is quite at odds with the rela-

tionship we have been trying to foster with the patient. They are often used as part of a naive approach, with an oversimplified view of what is, in reality, a very complex situation; and the results, which seem deceptively objective, often lead to unwarranted conclusions about the patient.

In summary, we have described the two extremes in the approach to the diagnostic interview, and have presented our contention that, while being therapeutically oriented, the first hour with the patient should be primarily diagnostic. We have reviewed the areas that should be covered in the initial interview and have discussed some of the general principles and elements involved, such as the feelings patients often bring to the hour, and the value of observing the patient and allowing him the initiative in telling his story. We have discussed our doubts as to the value of formal tests which interfere with the all-important relationship we have been striving to establish with the patient.

In conclusion, it may be again observed that the initial, or "diagnostic," interview with the patient, like all psychiatric interviews, cannot be conducted according to any simple formula. The interview must be highly individualized and guided by the developing relationship of the patient with the doctor. While in this respect the interview is psychotherapeutic, it is to be emphasized again that the purpose of the initial interview should be primarily diagnostic and evaluative, and only secondarily therapeutic. It is to be noted, however, that generally the most effective approaches to preliminary understanding are indirect, and not the more probing, categorical techniques. Thus, the general principles of psychotherapy guide us in the initial interviews; it is only the aim or goal of the interview, not the technique, which differs fundamentally from that of most psychotherapeutic interviews.

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CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

A Clinical and Neuropathologic Report

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THERE is a disease of man which is most typically manifested as a gradually progressive weakness of the muscles of the eyelids and of the external muscles of the eyeballs. The disease begins insidiously in early life (before the age of 30) and gradually involves more and more of these muscles until finally, after many years (30 to 40), severe ptosis and external ophthalmoplegia are present. The process may be bilateral or unilateral; it may be asymmetric in degree of involvement; progress of the disease may stop temporarily or permanently at any point, but remissions do not occur; the pupils remain unaffected; family incidence has been noted, and other muscles of the face, limbs, or trunk may show a similar kind of progressive weakness and wasting. The literature on this disease has recently been summarized by Kiloh and Nevin,[1] and it is they who have furnished a full and satisfying description of the signs and symptoms of this condition.

The problem of etiology is still far from settled. Among other factors, this stems from a disagreement as to the pathologic findings in the disease. It is postulated by some that the atrophy and weakness of the muscles of the eyelids and eyeballs are the result of neuronal disease. Thus, the condition has been called "chronic progressive nuclear ophthalmoplegia." On the other hand, it has been considered to be due to a primary degeneration of muscle tissue, and so the condition has been called "progressive dystrophy of the external ocular muscles," "ocular myopathy," or "chronic dystrophic ophthalmoplegia."

In favor of the "nuclear" theory are the following observations:

1. In the various classical forms of progressive muscular dystrophy, involvement of the muscles of the eyelids and/or of the extraocular muscles is rare.

2. Pathologic reports in two cases * purport to show neuronal disease in the nuclei of the third, fourth, and sixth cranial nerves of the brain stem.

Favoring the "myopathic" theory are the following observations:

1. While they are admittedly uncommon, cases of muscular dystrophy have been reported in which the muscles of the eyelids and the eyeballs have been involved.[5]

This study was partially supported by the Kirby-McCarthy Fund.

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Read in part before the Seventy-Eighth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 17, 1953.

* References 2, 3, and 4.

2. "In a quarter of the recorded cases [of chronic progressive external ophthalmoplegia], various other muscles have been involved," [1] especially the orbicularis oculi, but also other facial muscles, muscles of mastication, neck muscles, shoulder girdle muscles, proximal muscles of the upper limbs, and even muscles of the pelvic girdle and lower extremities.

3. In the two pathologic studies † which are claimed to support the "nuclear" theory, the nuclei of the third, fourth, and sixth cranial nerves in this condition showed neuronal changes which seem not at all compatible with the degree of clinical effect; the intramedullary and extramedullary structure of the third, fourth, and sixth cranial nerves in these cases was unchanged, and inadequate histologic attention was given to the affected extraocular muscles.[1]

4. Biopsies of muscles of the eyelids and eyeballs in cases of this disease have shown changes which strongly suggest the myopathic nature of the process.[1] Biopsies of other clinically uninvolved muscles in this disease have shown early myopathic changes.[1]

5. Finally, a recent neuropathologic study of a typical case [6] has furnished a more carefully investigated case indicating a myopathy.

Because of these differences of opinion, it was felt that a report of the findings in the brain stem, cranial nerves, and extraocular muscles in a typical case might be of value. Our findings seem to suggest that the basic disease process is not neuronal or neural, but, rather, muscular, in origin.

REPORT OF A CASE

History.—J. C. F. was first seen by one of us (G. A. S.) on April 21, 1950, at the request of Dr. George C. Crillman. The patient was then 63. He gave a history and presented signs and symptoms indicating two different and unrelated neurologic conditions.

1. Six months previous to this initial visit, the patient had begun to have bilateral supraorbital headaches. On April 13, 1950, poor control of his right lower extremity developed. This was followed by a motor and sensory focal seizure involving only this extremity, with a residual feeling of numbness of short duration and then complete recovery. He thereafter had a series of such attacks up to April 20.

At this time the significant neurologic findings were slight weakness of the right lower extremity, slight impairment of touch and pain perception in the right lower extremity, impairment of position sense in the right large toe, slight dyssynergia of the right upper extremity, and increased activity of the deep reflexes on the right side. His blood pressure was 160/90.

A roentgenogram of the skull on June 8 showed that the pineal body was not calcified. No other abnormality was noted. An electroencephalogram on May 19 showed diffuse 4 to 6 per second waves and a focus of slow-wave discharges from the tip of the left temporal lobe.

The patient was chiefly concerned about his continuing sensory attacks. They were often intensely annoying and unpleasant and were always limited to his right lower extremity. In June, 1950, there developed an erysipeloid of Sulzberger on his right foot and leg. His sensory attacks became more frequent and were poorly controlled by anticonvulsant medication. Finally, hospitalization was needed for recovery from this infection.

By September, 1950, Jacksonian seizures had developed, which involved his right upper extremity and the right side of his face. The right extremity became weak. He became slightly confused and somnolent. A mixed dysphasia developed. There was no papilledema. On Nov. 5, 1950, a left carotid arteriogram was made. The anterior cerebral arteries were shifted to the right. On Nov. 6 Dr. Francis C. Grant performed a left craniotomy, but no tumor could be

† References 2, 3, and 4.

found. The patient's postoperative course was difficult, but he recovered sufficiently to leave the hospital, with right hemiplegia and motor aphasia. The cranial decompression area was full but not bulging.

The patient's hemiplegia persisted, and his aphasia became more mixed. The decompression area was bulging and tense. He became somnolent, then stuporous, and went into coma. He died on Jan. 20, 1951.

Postmortem examination revealed an enlarged left cerebral hemisphere. This enlargement was due chiefly to marked cerebral edema but resulted also from an infiltrating neoplasm deep in the left parietal lobule. On histologic study the tumor was identified as a spongioblastoma polare.

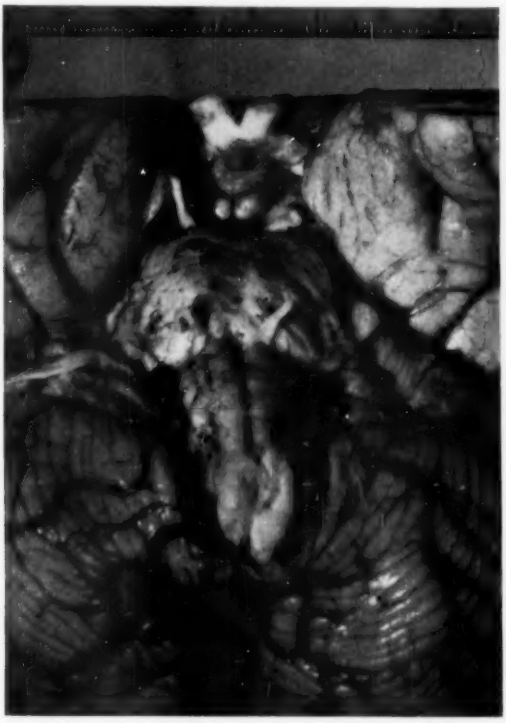

Fig. 1.—Photograph of the base of the brain and brain stem of our patient, J. C. F. This view clearly shows the oculomotor (III) and abducens (VI) nerves presenting in their normal locations. We felt that grossly they seemed smaller than usual.

2. At the age of 27 or 28, he first became aware of drooping of his left upper eyelid. He believed his right upper eyelid did not begin to droop until he was about 41 years of age. The drooping was gradually progressive. Over the years, he required several operations on his upper eyelids to relieve this annoying symptom. Just when and how the difficulty in the movements of his eyeballs began was hard to determine, even after repeated and careful questioning of the patient. Apparently, it began insidiously and progressed very slowly. He had noted double vision occasionally at least three years before the sensorimotor attacks developed. Even then the diplopia was not severe or of long duration. He was not sure how many years it had been that he had to move his head to see things.

There was no family history of any such difficulty.

Examinations in 1950 resulted in the following pertinent findings: There was bilateral ptosis. To see, the patient had to tilt his head back. His forehead was invariably wrinkled, with the eyebrows elevated. The palpebral fissures were markedly narrowed. The patient was unable voluntarily to elevate his upper eyelids. The pupils were equal, regular, and round and reacted well to light and poorly to attempted accommodation-convergence. The eyeballs were always in the primary position and showed practically no rotation or convergence. On upward gaze, the eyeballs moved but slightly from midposition, and the right seemed to move a little more. On downward gaze, both eyes moved only a little, but again, the right a little more than the left. On right lateral gaze, the eyeballs did not move at all. On left lateral gaze, there was only slight movement, which was a bit better in the right eye. This was true on both voluntary and reflex conjugate movements. The other cranial nerves were intact.

The left thenar eminence was smaller than the right. The muscles of the left forearm were smaller. There were no fasciculations. Muscular power and tone were good throughout the upper extremities despite the muscle wasting.

The routine laboratory tests of the blood and urine were essentially within normal limits. Blood tests for syphilis gave repeated negative reactions. On Oct. 4, 1950, his cerebrospinal fluid was under a pressure of 185 mm. of water and contained no cells, but the protein content was 101 mg. per 100 cc.

Postmortem Findings.—Gross Description (Fig. 1): The third nerves were found arising at the interpeduncular fossa. The right one seemed to be smaller than the left. In the space of Bichat the fourth cranial nerves were found as thin neural strands. The sixth cranial nerves were observed to arise from the pontomedullary boundary, and of these the left one seemed to be the smaller. Other than bilateral uncal grooves and cerebellar tonsils, the structures at the base of the brain revealed nothing unusual.

Microscopic Description: The brain, spinal cord, and muscles were fixed in 10% formalin. The brain stem was embedded in celloidin and cut serially. Some portions of the muscles were embedded in paraffin. Tissues were stained by the Weil technique for myelin, with thionine for the Nissl bodies, with hematoxylin and eosin, and by the Protargol (strong protein silver) method of Bodian.

Nucleus of the oculomotor nerve (III). The Edinger-Westphal nuclei, the nucleus of Perlia, and the motor nuclei could be readily distinguished and presented their usual relationships. The cellular population revealed no change from the expected normal (Fig. 2).

The motor neurones showed a Nissl pattern clearly distinguishable as motor in type. The Nissl bodies were definite, distinct condensations scattered in the perikaryon. The nuclei were round and vesicular and occupied a normal position in the cell bodies. The nucleoli were round densities with a central pale spot, and they, too, occupied a normal position within the nuclei. Three abnormalities were noted in the motor neurones: 1. We gained the impression that these motor neurones were perhaps smaller, definitely less angular, and hence rounder, than similarly stained cells of control specimens (Fig. 3). This seemed to be due in part to the lack of staining of the chromatin material in the dendrites. Dendritic prolongations from the cell bodies were not as frequently seen as in the controls. 2. Almost every neurone contained clumps of a granular pigment in its perikaryon. The pigment had a yellow-brown color in the Nissl stain. The material usually was found in one clump, but an occasional cell showed the pigment more diffusely scattered in the cytoplasm. Some cells contained two such groups, at opposite poles of the cell body. The pigment seemed to displace the Nissl substance. The amount of pigment material varied considerably from cell to cell. When the quantity was large, it displaced the nucleus a bit. 3. There were in some cells round, empty vacuoles. These were located in the cytoplasm, and the Nissl substance was clearly displaced by the vacuoles. The vacuoles were not as frequently observed as the intracellular pigment collections. The vacuoles were nearer the cell membrane, which they often distended. The vacuoles seemed to be independent of the pigment changes.

The neurones of the nuclei of Edinger-Westphal and of Perlia showed no abnormalities. These cells showed no pigment inclusions and no vacuoles.

There were no indications of vascular changes or of inflammation within or in the vicinity of the various oculomotor nuclei. The glial cells revealed no changes.

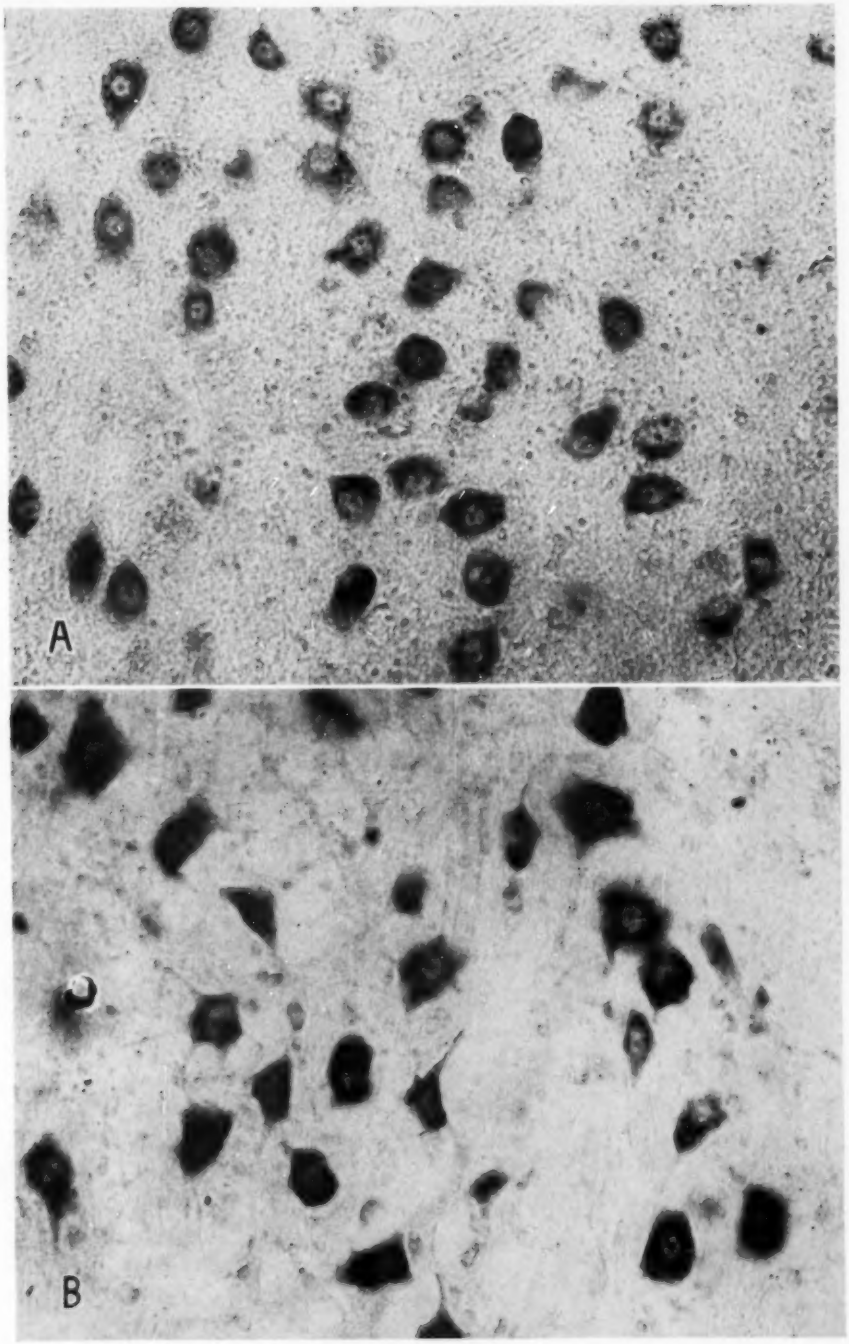

Fig. 2.—*A*, portion of an oculomotor (III) nucleus of our patient, showing the cellular population. Compare this with *B*, which is a portion of this nucleus of a normal person. Thionine stain; × 290.

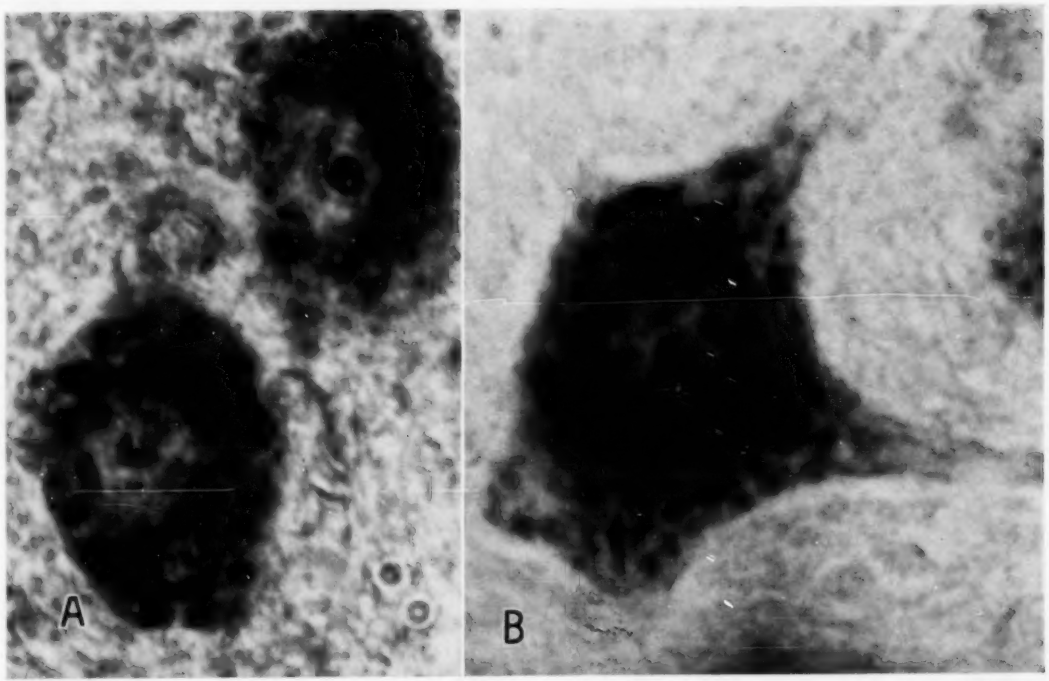

Fig. 3.—*A*, neurones of the oculomotor (III) nucleus of our patient, showing preservation of the Nissl bodies, the smaller, rounder perikaryon, and the failure of the dendritic processes to stain. Compare with *B*, showing a neurone of this nucleus from a normal control. Thionine stain: × 1,450.

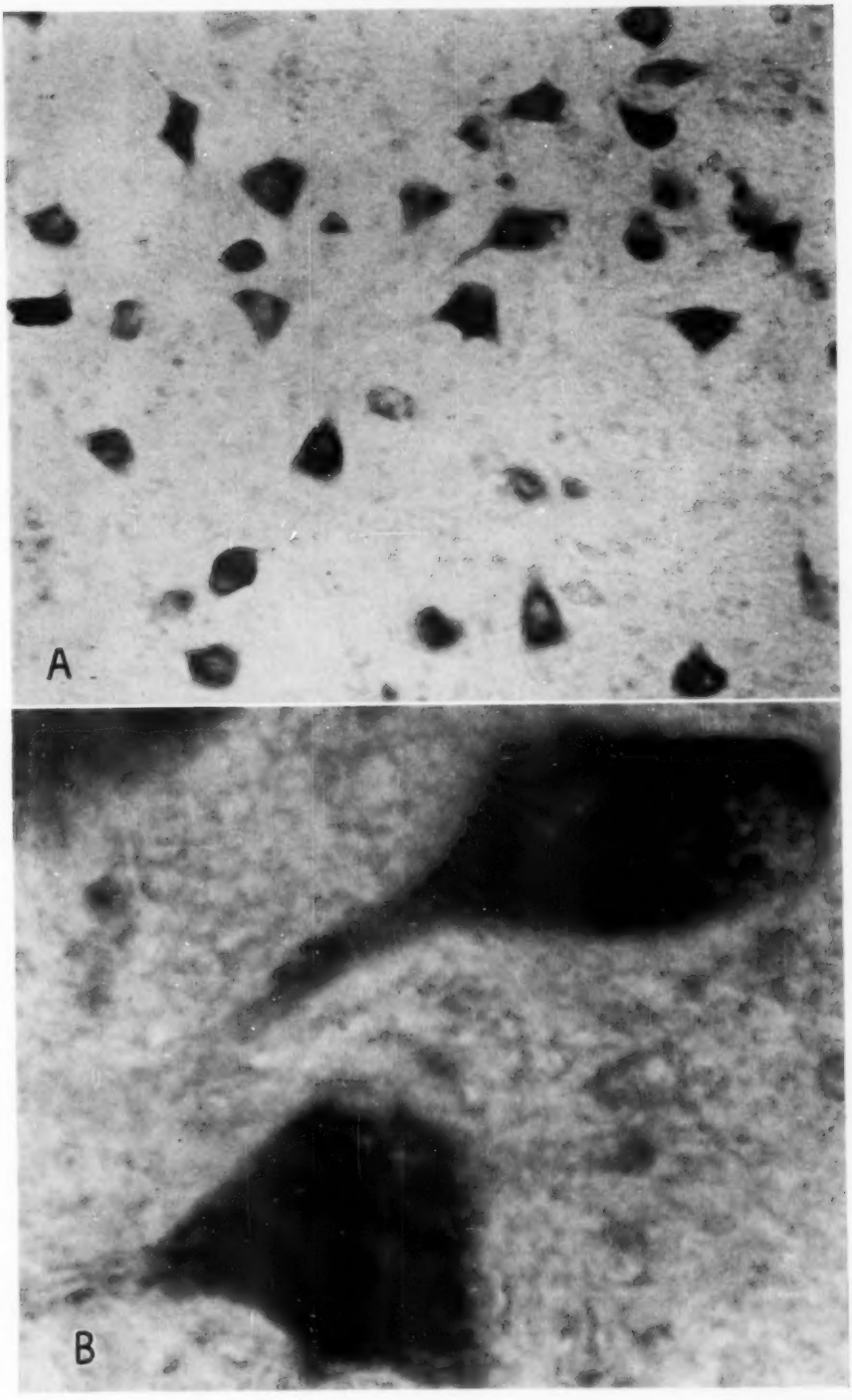

Fig. 4.—*A*, portion of a trochlear (IV) nucleus of our patient, showing the neuronal population. Thionine stain; × 290.

B, neurones from field shown in *A*. Note the well-preserved Nissl bodies. Both neurones show vacuoles in their cytoplasm. Thionine stain; × 1,450.

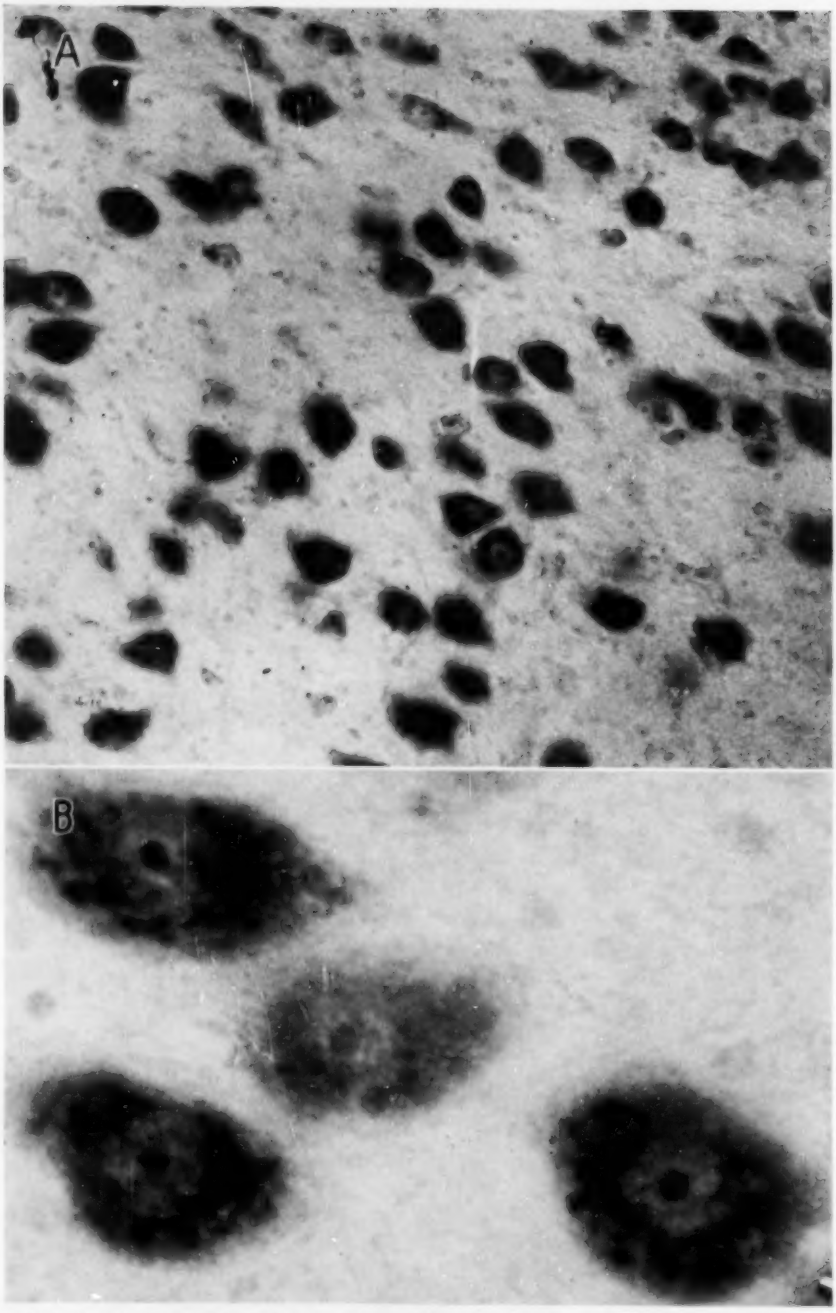

Fig. 5.—*A*, portion of an abducens (VI) nucleus of our patient showing the cellular population. Thionine stain; × 290.

B, neurones from field shown in *A*. Here, too, the neurones were round and less polygonal, and the dendritic processes were often not visible. Thionine stain; ×1,320.

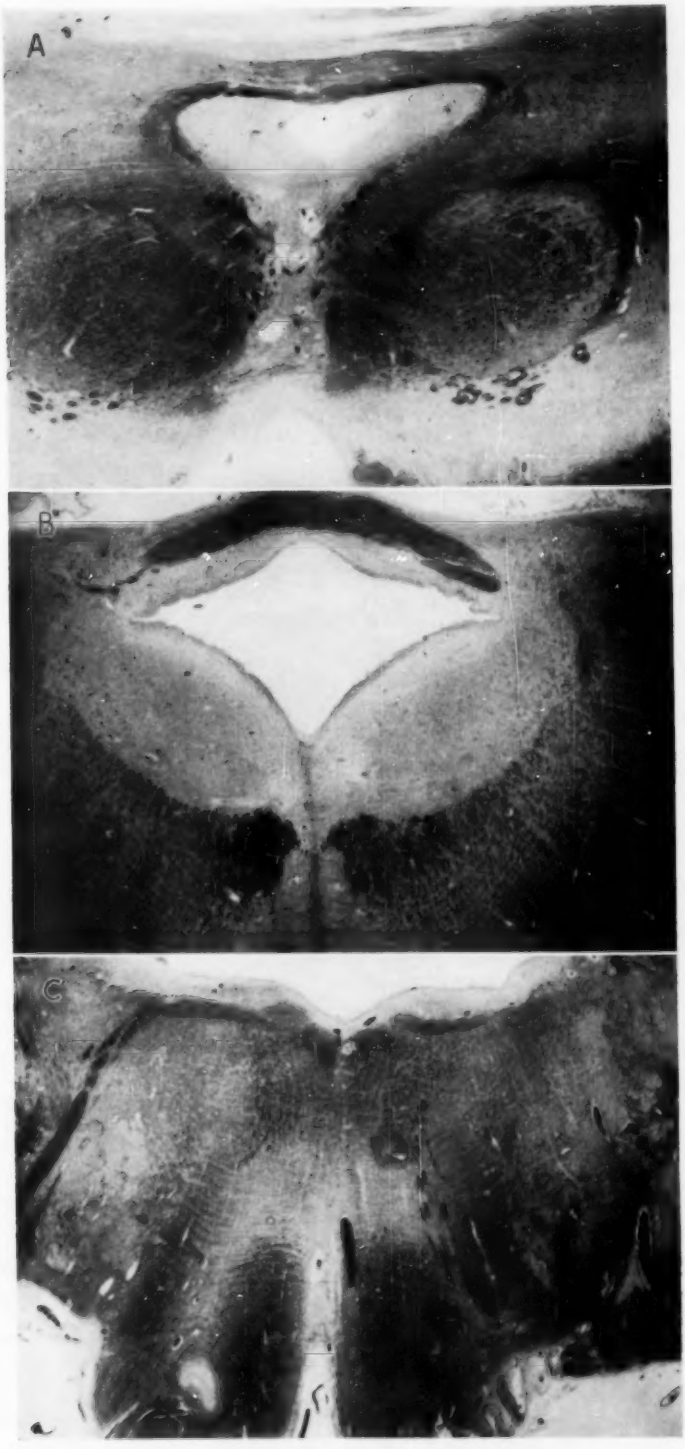

Fig. 6.—*A*, mesencephalon showing the intra-axial portions of the oculomotor (III) nerves as they course ventrally and laterally from their origin in the nuclei. Weil stain; × 45.

B, roof of the aqueduct of Sylvius showing the decussation of the trochlear nerves. On one side the fibers can be seen coursing dorsad preparatory to their exit from the pons. Weil stain; × 45.

C, pontomedullary area showing the intra-axial fibers of the abducens nerves in their ventrolateral course from their nuclei. Weil stain; × 45.

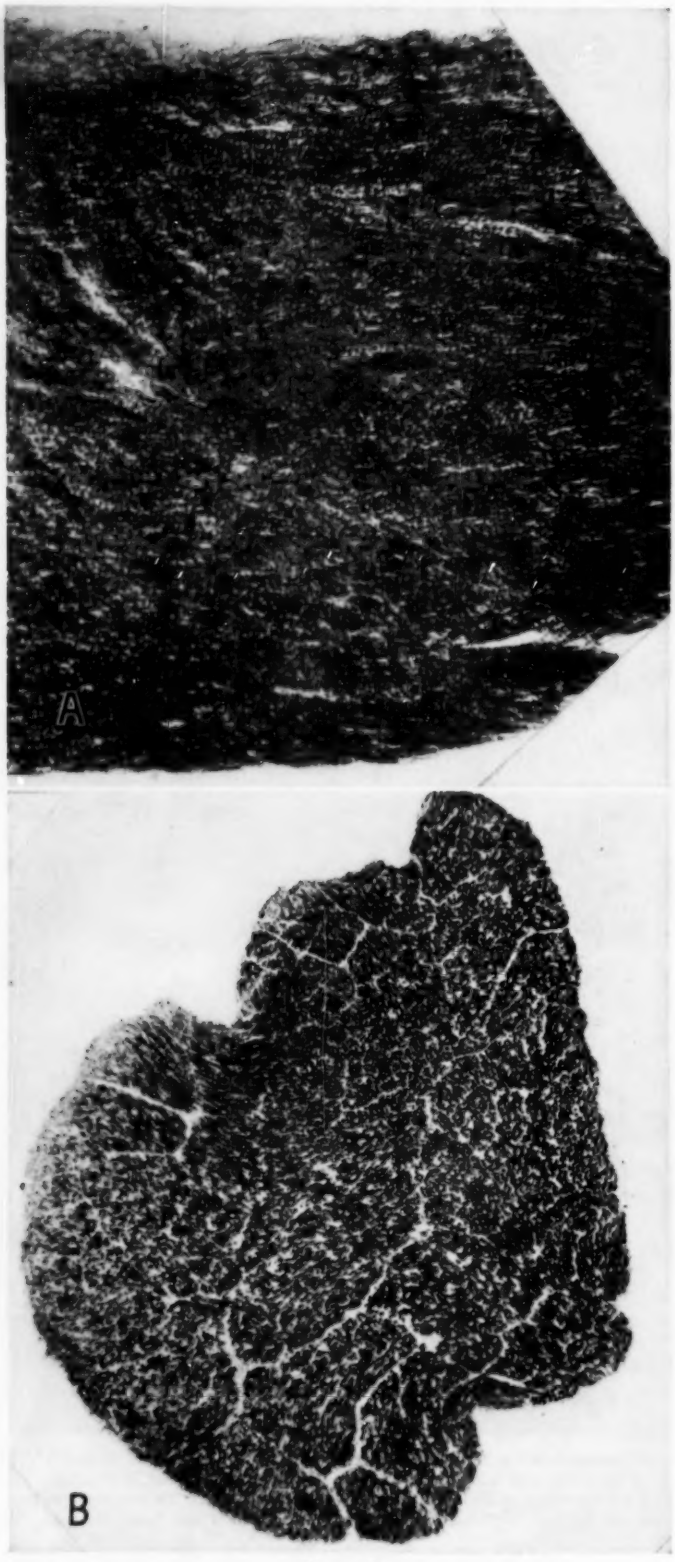

Figure 7

Nucleus of the trochlear nerve (IV). The fountainoid nucleus and the trochlear nuclei could readily be distinguished and showed their usual relationships.

The motor neurones seemed to be abundant (Fig. 4*A*), and they were of the usual shape. Again, there seemed to be no notable pathologic change in the trochlear neurones. The Nissl substance was contained as large, definite bodies scattered throughout the cytoplasm in the pattern characteristic of motor cells. The nuclei were large, clear, vesicular structures, appropriately located in the perikarya. Their nucleoli were dense balls, normally located, and, again, showed the clear spot in their centers. Here, too, the neurones seemed smaller, less angular, and rounder, with poor visualization of dendritic processes (Fig. 4*B*). There was, again, pigment in the cell bodies, often near the periphery of the cell, occasionally more diffusely distributed near the nucleus. Almost all the cells contained this pigment, but the impression was gained that it was not as abundant as that seen in the oculomotor neurones. One difference here was that vacuolation of neurones was not present, as it was in the motor cells of the third cranial nerve nuclei.

The large cells of the fountainoid nucleus were found to contain clumps of the pigment seen in the motor neurones of the trochlear nerve.

Again, no signs of vascular disease, inflammatory disease, or glial change were noted.

Masticator nucleus (motor V). The nuclei were readily identified, showing their usual position and relationships.

The large, multipolar neurones were readily seen, with their well-stained dendrites. Only an occasional cell contained a vacuole. The cell bodies also contained pigment, as described before.

On one side, laterality not known, the large motor neurones of this nucleus showed considerable chromatolysis. This change was more marked in the cells of the dorsal portion of the nucleus. All degrees of severity of change were noted, and not every cell was involved, for a healthy-looking cell would appear beside a chromatolyzed neurone. The opposite masticator nucleus showed no such change.

Nucleus of abducens nerve (VI). The abducens nuclei were readily identified in the floor substance of the fourth ventricle. The nuclei seemed to be in the expected position and relationship with other structures. The cell population did not seem to be altered from the expected (Fig. 5*A*). The neurones were small, certainly smaller than the other motor neurones of the brain stem. They seemed to be less angular, perhaps more rounded, in general (Fig. 5*B*). There was a greater variation of density of staining in these neurones than in the nuclei of the oculomotor nerves and the trochlear nerves. Again, the dendritic processes were not abundantly visible. The chromidial material was distributed in the motor cell pattern. Cellular abnormalities were noted as follows: 1. Clear vacuoles were present in some neurones. Sometimes only single vacuoles were noted. Occasional cells contained many large vacuoles, distorting the cell contour. 2. Cytoplasmic pigment masses were noted as before. 3. Chromatolyzed neurones, showing peripheral condensation of Nissl substance and displaced nuclei and nucleoli, were seen here. A few neurones showed loss of peripheral Nissl masses with preservation of perinuclear Nissl bodies. A few neurones were almost devoid of any Nissl substance and were pale in appearance and outline—"ghost cells." While by no means frequent, such neuronal changes were more abundant in the abducens nuclei than in the nuclei of the oculomotor and trochlear nerves.

Nucleus of facial nerve (VII). The nuclei were readily identified in their usual relationships. The cell population seemed unchanged.

The neurones were large, polygonal, multipolar cells. Their dendrites contained chromidial material, so that they could readily be followed some distance from the cell bodies. The Nissl pattern consisted of large masses of this substance, as seen in the somatic motor neurones. Nuclei and nucleoli showed no changes. Almost every cell contained a focal mass of granular pigment, as described before. No vacuoles were seen. No vascular or glial changes were observed.

EXPLANATION OF FIGURE 7

Fig. 7.—*A*, longitudinal section, oculomotor (III) nerve, showing normally myelinated nerve fibers. Weil stain; × 75.

B, cross section, oculomotor (III) nerve. The intact myelin sheaths are strikingly shown by this view. Weil stain; × 75.

Nucleus ambiguus (IX and X) and hypoglossal nucleus (XII). These somatic motor neurones showed no change other than the intracytoplasmic pigment masses, although these were not as abundant here as in the other bulbar motor nuclei.

High thoracic level of spinal cord. The anterior horn cells showed cell shrinkage of moderate degree with preservation of the Nissl masses. Most of these neurones contained the masses

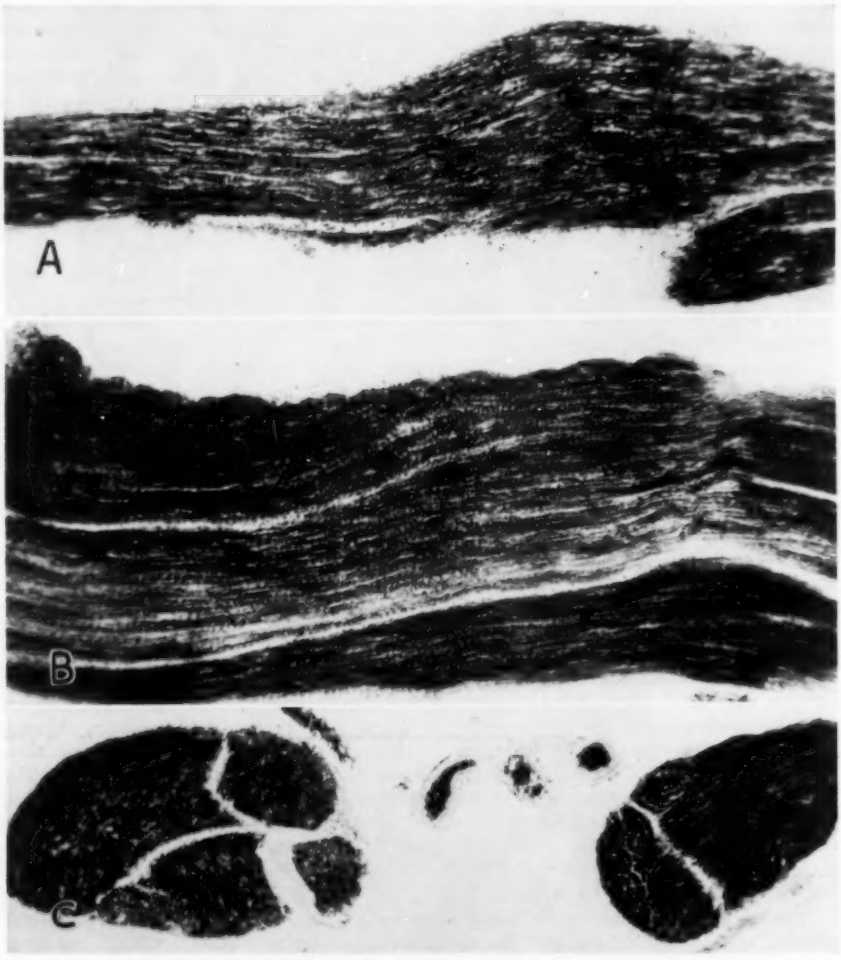

Fig. 8.—*A*, longitudinal section, trochlear (IV) nerve, showing preserved myelination. Weil stain; × 75.

B, longitudinal section, abducens (VI) nerve, and *C*, cross-oblique sections of the same nerve, showing the intact myelination. Weil stain; × 75.

of pigment described above. Indeed, some cells seemed to have a tremendous quantity of this pigment material within their cytoplasm.

Intra-axial portion of oculomotor nerve (III). Myelinated fibers arising from the oculomotor nuclei in the central gray matter of the mesencephalon could readily be traced as they ran

between the bundles of the medial longitudinal fasciculus and then coursed through and medial to the red nuclei (Fig. 6*A*). There were no indications of demyelination.

Intra-axial portion of trochlear nerve (IV). The myelinated fibers of the trochlear nerve in their decussation in the roof of the aqueduct were readily identified (Fig. 6*B*). No evidence of demyelination was noted.

Intra-axial portion of abducens nerve (VI). In Weil preparations, the myelinated fibers of the abducens nerves could be identified running ventrally and a little laterally through the tegmentum of the pons. As usual, they consisted of several bundles of fibers, which took an oblique course to emerge just lateral to the pyramids at the lower level of the pons (Fig. 6*C*).

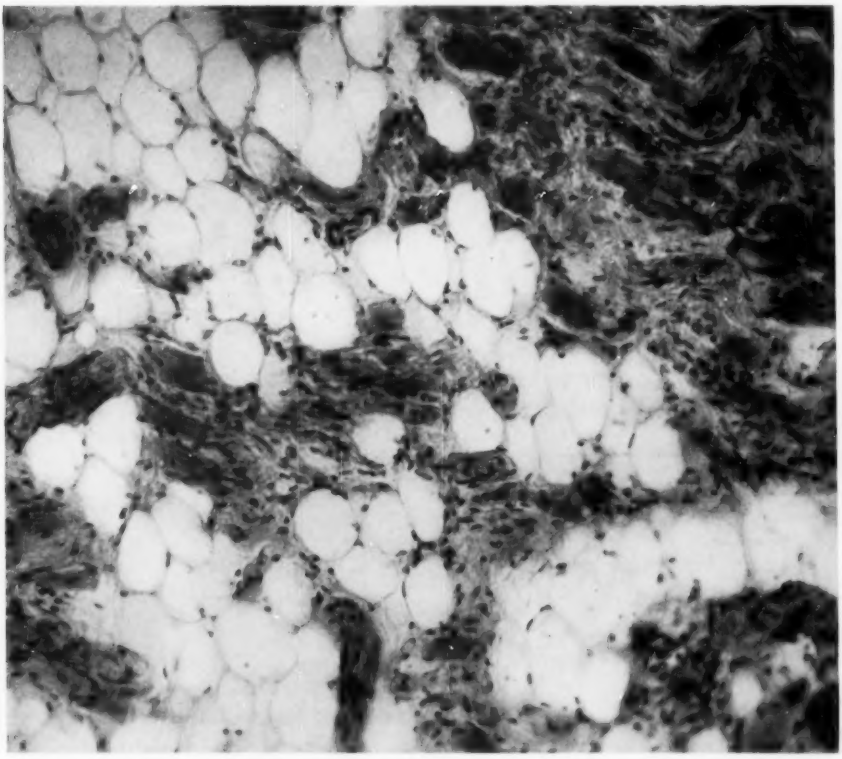

Fig. 9.—Left superior oblique muscle. Note the patchy portions of degenerated striated muscle fibers enclosed by connective tissue and fat. Hematoxylin-eosin stain; × 290.

No areas of demyelination were noted along the course of these fibers, nor did they seem reduced in number; and at root exit zones no changes indicating damage to these fibers could be noted.

Extra-axial portion of oculomotor nerve (III). With the hematoxylin-eosin stain, the neurokeratin framework was well defined and axis cylinders could be readily seen in the nerve fibers. There was perhaps an overabundance of nuclei visible. No changes were noted in the vasa nervorum.

In the myelin preparations, no areas of demyelination were seen (Fig. 7). The Schmidt-Lantermann incisures were very prominent.

Extra-axial portion of trochlear nerve (IV). In the hematoxylin-eosin preparations, the nerve fibers stained readily and perhaps seemed a little more compact in structure than did the

oculomotor nerve. The nuclei were not quite as abundant as those of the third nerve.

The myelin sheaths stained well. Again, no demyelination was observed (Fig. 8*A*).

With the axis cylinder stain, counts were made of the nerve fibers of the right trochlear nerve and of the nerve fibers of the same nerve from a normal control of about the same age. No significant difference in the number of fibers in the trochlear nerves was noted.

Extra-axial portion of abducens nerve (VI). In the hematoxylin-eosin sections, the nerve fibers stained well. The neurokeratin framework and the axis cylinders were well seen. The nuclei, again, were not as abundant as in the oculomotor nerves.

The myelin sheaths stained well. No demyelination was noted (Fig. 8*B*).

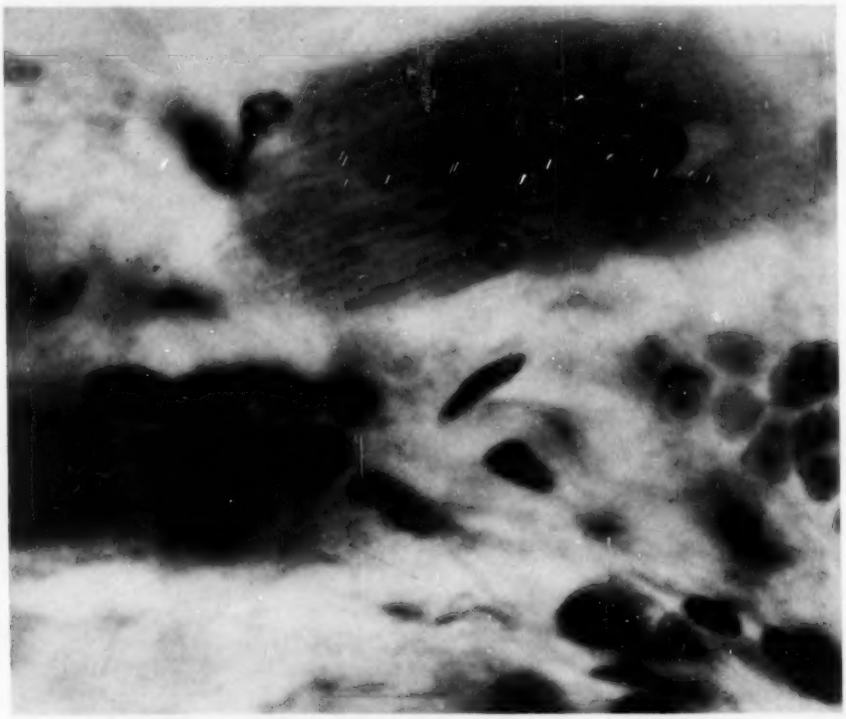

Fig. 10.—Left superior oblique muscle. This shows the dramatic changes that had been, and apparently were still, occurring in this striated muscle. The myofibrils were swollen and the cross striations lost. The increased nuclei are evident. Hematoxylin-eosin stain; × 1,620.

Left superior oblique muscle. In the hematoxylin-eosin stain, the sections of this muscle consisted of areas of fat cells, masses of dense abundant fibrous tissue, numerous nerve trunks, a few blood vessels, and portions of striated muscle scattered irregularly in the strands of connective tissue and fat. The areas of fat cells were often very extensive, with perhaps only nerve fibers running through them. But oftener the fat cells appeared between islands of fibrous tissue (Fig. 9). Scattered in the fibrous tissue, often near degenerated fibers, and especially near larger blood vessels, were phagocytic cells. Some of these were plasma cells; others had the dense nuclei of tissue macrophages. Their cytoplasm contained eosin-stained particles. The fibrous tissue was often quite fibrillar, but for the most part contained many nuclei. This was particularly true about and near the degenerating muscle fibers. Hence there were areas of condensation of nuclei—of young fibroblasts, of phagocytic cells, and of muscle fibers.

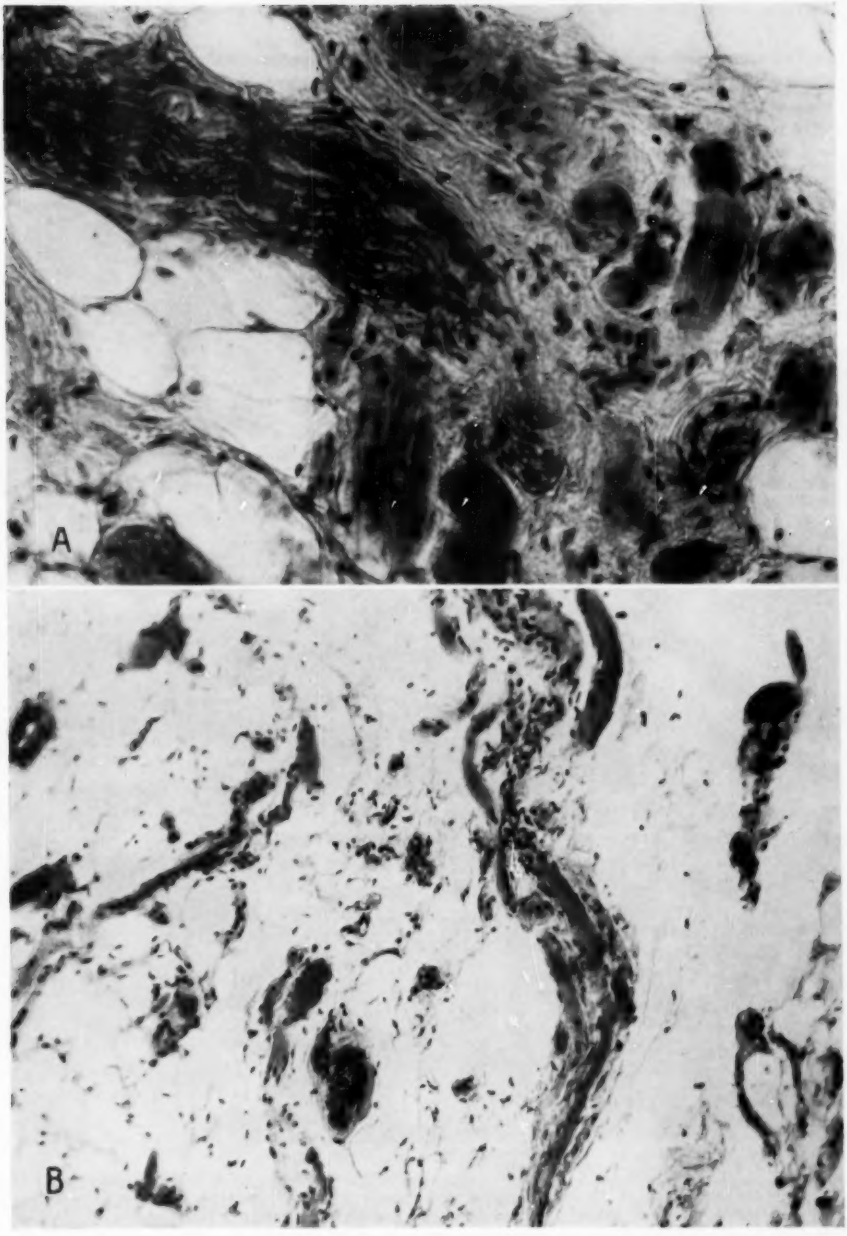

Fig. 11.—*A*, left superior oblique muscle. Note the bundles of myelinated fibers running in the fatty and connective tissue. Portions of degenerated muscle fibers are also seen. Weil stain; × 333.

B, left superior rectus muscle. The intense destruction of the striated muscle fibers, the remaining few abnormal fibers, the connective-tissue overgrowth, all of these contained in fat tissue—these changes are readily observed in this section. Hematoxylin-eosin stain; × 240.

The changes in the muscle cells were severe. A few healthy-looking muscle fibers could always be found. The pathologic changes were variable in degree from place to place, as they were even within a single muscle fiber. Some of the muscle fibers were greatly swollen; some were very small. The myofibrils often lost their cross striations. They were often swollen and separated. In places the myofibrils faded out and the muscle fibers stained a homogeneous pink.

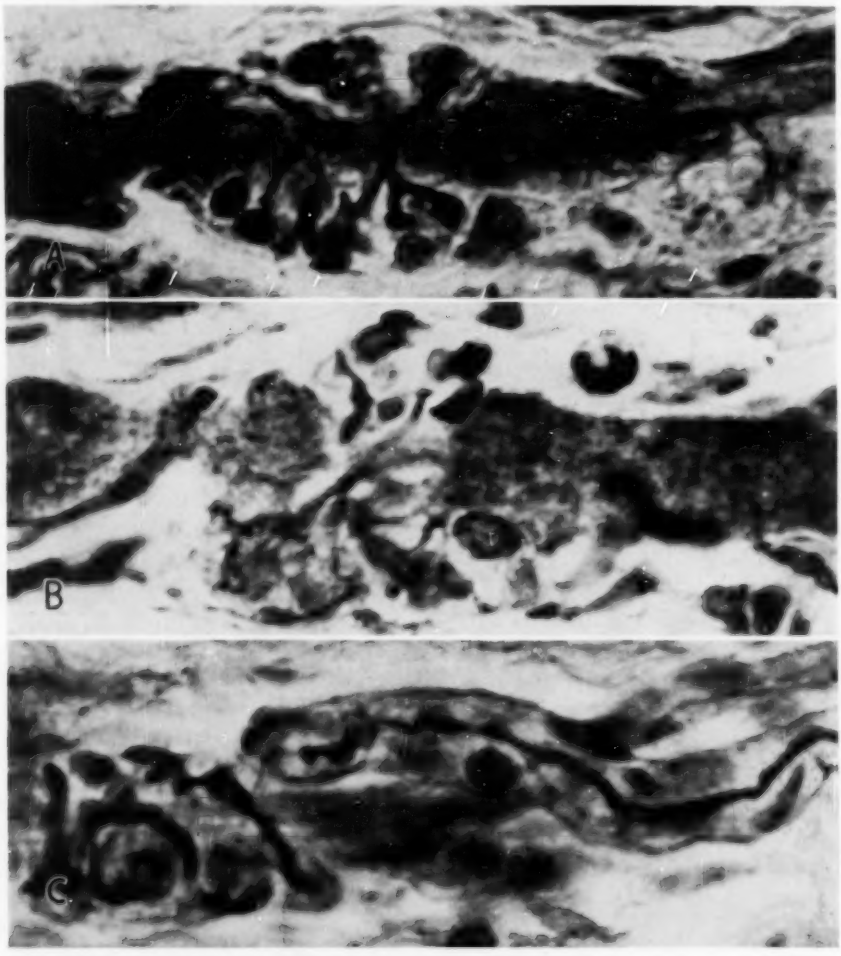

Fig. 12. Right lateral rectus muscle.

A, motor end-plate of swollen, degenerated muscle fiber. *B*, motor end-plate of swollen, granular muscle fiber. *C*, nerve fiber and its motor end-plate to a muscle fairly well preserved at this site. Bodian's Protargol (strong protein silver U. S. P.) stain; × 1,350.

In other areas the muscle fibrils were fragmented and the sarcolemmal sac contained only weakly staining granules (Fig. 10).

The blood vessels showed no changes.

In the myelin preparations, numerous bundles of myelinated nerve fibers were readily seen (Fig. 11*A*). These were surrounded by the fatty tissue or the connective tissue. They were

found in fairly large bundles of large fibers, but single large and small nerve fibers could be seen running in the connective tissue or coursing between the muscle fibers. There was nothing noted in the myelin sheaths to indicate Wallerian degeneration; the Schmidt-Lantermann segments were prominent.

With Bodian's Protargol method, the axis cylinders stained well within the nerve bundles. They showed no fragmentation or nodule formation. In the fibrous tissue, in the fat, and along the remaining muscle fibers, thick and fine axis cylinders were abundantly found. Elaborate spiral nerve endings were found encircling some muscle fibers (though degenerated). A few very fine fibers were found to end on capillary walls. Although not as abundant as in the other extraocular muscles we examined, motor nerve endings were readily identified. These were found even on greatly degenerated and altered muscle fibers.

Left superior rectus muscle. With the hematoxylin and eosin stain, this muscle presented essentially the same pathologic changes as those described for the superior oblique muscle, viz., a few degenerated or healthy muscle fibers enclosed in a meshwork of fat and connective tissue (Fig. 11*B*). Again, nerve bundles and fibers were abundant.

With the myelin stain, well-myelinated nerve fibers were found singly and in bundles running in the fatty tissue, in the connective tissue, and between the degenerating muscle fibers.

With the Protargol method of Bodian, the axis cylinders stained well. Nerve fibers could be followed running for long distances beside degenerating or relatively well-preserved muscle fibers. Here especially, elaborate motor end-plates could be identified on the degenerating muscle fibers.

Right lateral rectus muscle. In the sections of this extraocular muscle, the histologic picture was much the same, with preserved muscle fibers and variably changed muscle fibers present in a stroma of fat and fibrous tissue. As before, the nerve fibers were abundantly seen.

The Bodian stain revealed well-defined motor end-plates on muscle fibers often severely degenerated (Fig. 12).

Pectoralis major muscle. No abnormalities were observed in the portions of this muscle that were stained by the techniques previously mentioned.

Ciliary ganglia. Both ciliary ganglia were available for study. The myelin stain revealed bundles of finely myelinated nerve fibers coursing between and about the neurones. There was no increase in the capsular nuclei or in the interstitial connective tissue. The ganglionic cells varied in size. The nuclei showed well-defined nucleoli. Occasional cells showed displaced nuclei. The nuclei were round and oval; some nuclei stained rather darkly. The Nissl material stained variably—sometimes rather darkly and other times very lightly. The Nissl material was found to be condensed about the nuclei in some few cells, but for the most part was spread throughout the cytoplasm. It was never condensed at the cell periphery. A very few cells were found to have discrete black cytoplasmic pigment. No regular abnormal cell changes were noted. No binucleated cells were observed.

COMMENT

Findings in Muscles.—For some time there has been a difference of opinion as to the validity of a histologic distinction between the wasted muscle of muscular dystrophy and the atrophic muscle following motor neural or motor neuronal destruction. Durante [7] concluded that on the basis of the microscopic examination of the diseased muscle tissue alone the identity of a "primary" myopathy, as against a "secondary" muscle disease, could not be established. Slauck [8] decided that if the changes were not too advanced, denervated muscle could be distinguished from dystrophic muscle—in the former the degenerated muscle fibers were found in small bundles, whereas in the latter normal muscle fibers were found side by side with degenerated fibers and not in groups. Hassin [9] described "definite changes" in the muscles in progressive muscular dystrophy.

> The changes are in the form of atrophies, hypertrophies, loss of striations, myofibrillary disruption, obliteration of Cohnheim's fields, hyalinization, fatty metamorphosis (lipomatosis), all resulting in a formation of a connective tissue scar (fibrosis).

Bowden and Gutmann [10] stated that "the late changes in dystrophic muscle fibers are identical with those observed in the final stages of denervation atrophy." Therefore, they concluded, "no clear differentiation between primary and secondary myopathies is possible when the state of the muscle fibers is considered alone." But they emphasized:

> A distinction can be made when the innervation is observed. In cases of muscular dystrophy the changes in the muscle fibers are found while innervation is still intact or a pattern of terminal abortive regeneration is present. In cases of atrophy of neural origin, denervation is indicated by the empty nerve trunks.

Previously, Falin and Kanarejkin [11] had made similar observations.

More recently, Kirschbaum [12] and Arieff and Kirschbaum [13] have described the many histologic changes occurring in neuromuscular diseases. As to the histologic criteria needed to establish the diagnosis of a primary myopathy, they emphasized the "integrity of the nerve fibers" in the atrophied muscle, the "well-preserved motor end-plates in and about degenerating muscle fibers," and "the absence of a preceding retrograde degeneration of the axons with proliferation of the Schwann cells."

From a related viewpoint, Batten,[14] Spiller,[15] and Bruce,[16] among others, observed the preservation of muscle spindles amidst the usual degenerative changes in muscular dystrophy.

It would seem, therefore, that, to gather evidence to support the idea that progressive external ophthalmoplegia is a form of muscular dystrophy, the neural elements within the extraocular muscles should be studied. However, it must first be realized that, while these muscles are striated, they present an innervation unlike that of other striated musculature.[17] Until recently,[18] muscle spindles had not been identified in the extraocular muscles of man, although they had been readily found in such muscles of certain other species.[19] However, the muscle spindles of human extraocular muscle are different than the classical muscle spindle of Kühne described in other striated musculature in that their capsules are very thin and delicate and the whole structure is much smaller.[20] Then, too, they are found only in certain regions of these muscles,[18] being absent, or nearly so, from the middle third, where the motor end-plates, the nerve fibers, and the spiral nerve endings are abundant. Other nerve endings in the human extrinsic eye muscles have been described by Woollard [21] and Daniel [22]; whether the grape-like endings of Woollard and the spiral endings of Daniel subserve a motor or a sensory function is not yet clear. Motor end-plates are abundant in these muscles, there being 5 to 20 end-plates for each nerve fiber,[23] and they do not differ anatomically from the motor foot-plates of other striated muscles. That all the nerve endings in the extrinsic eye muscles of man are not motor in function is shown by the recent evidence of sensory responses arising from these muscles.‡

Another unusual thing about the extraocular muscles is their abundance of motor nerve fibers. Tergast [27] estimated that there was one nerve fiber for every three muscle fibers in the extraocular muscles. However, Cogan [17] thinks a more accurate estimate would be 1 nerve fiber for 10 muscle fibers. Since it has been estimated that there is 1 motor nerve fiber for each 140 muscle fibers [28] in other

‡ References 24, 25 and 26.

striated musculature, it will be seen that one can expect to find quite an abundant nerve supply in the extraocular muscles.

Applying all these findings and opinions to the study of the muscles of the eyeballs in our case, we can state first that the changes noted in the muscle fibers of our patient paralleled those changes described by others in cases of muscular dystrophy. There were atrophy of muscle fibers, swelling of muscle fibers, loss of muscle striations, hyalinization of muscle fibers, fragmentation of muscle fibers, phagocytosis of disrupted myofibrils, overgrowth of fat and connective tissue replacing the destroyed muscle fibers, preservation of some fibers, involvement of a single muscle fiber in varying degrees in different parts, etc. The stains for myelin and axis cylinders brought out well the abundant nerve fibers running in the devastated muscles. Indeed, in many areas the number of nerve fibers far surpassed the number of remaining muscle fibers. We were also able to demonstrate the motor endings described in the extraocular muscles, and we found them on obviously pathologic muscle fibers. We did not observe the various formations described by Bowden and Gutmann,[10] and interpreted by them to be abortive regenerative attempts of the fibers of the motor end-plates.

Findings in Nerve Fibers.—Integrity of the intra-axial and extra-axial portions of the motor nerves in muscular dystrophy has been the usual finding; yet changes in peripheral nerves and in anterior roots have been described. Holmes [29] noted that the ventral spinal roots were smaller than normal in his case of muscular dystrophy. He found a reduction in the number of the nerve fibers, while many of the remaining nerve fibers were atrophied and the connective tissue of the roots was increased. Similar changes were found in some of the peripheral nerves. He also referred to 13 other cases of muscular dystrophy from the literature in which various changes in the nervous system had been noted. Of these 13 cases, pathologic changes in the ventral spinal roots and/or the peripheral nerves were recorded in 5. Friesz [30] also found neurolemmal nuclei increased and endoneurial fibers thickened in the spinal roots in his case.

In our case, grossly, the oculomotor nerves, the trochlear nerves, and the abducens nerves appeared smaller than was expected. Yet when we counted the axis cylinders in the right trochlear nerve and compared the fiber count with a control, the difference was not significant. In the trochlear nerve there was an increase in nuclei. For the most part, however, the motor nerves were well preserved, containing large myelinated elements with no areas of demyelination or any other changes suggesting Wallerian degeneration.

Findings in Neurones.—The somatomotor neurones have been studied in cases of muscular dystrophy. In most cases, with careful study, no neuronal changes have been noted. For instance, Friesz [30] studied the spinal cord of a woman aged 52 (of a myopathic family described by Jendrássik) whose muscle disease began between the ages of 6 and 7 years. He found the size and number of the motor neurones to be the same as those of his normal control. The Nissl bodies in the ventral horn cells did not differ from his normal in any way. Spiller [31] noted that the motor neurones of the facial nucleus (VII) were intact in a case of marked wasting of the facial muscles. Landouzy and Lortat-Jacob [32] noted the same thing in their case, as well as the integrity of the ventral horn cells. Yet other observers have noted changes in the somatomotor neurones in well-established cases of muscular dystrophy. Holmes [29] studied the neuromuscular system of a girl aged

11 years who began to have her symptoms at the age of 1½ years. He found that the ventral horn cells were reduced significantly in number, were smaller in size, due to atrophy and shrinkage, and contained an excessive amount of pigment for her age. Bruce [16] found that the motor nerve cells of the "anterior cornua" showed "only slight atrophic changes," which he felt "would be compatible with a secondary atrophy." Most observers have concluded, as did Holmes,[29] that the neuronal changes could not be primary, but were probably a secondary reaction to the loss of the muscular portion of the neuromuscular unit. Kinnier Wilson [33] held that such neuronal changes "represent transitional forms with coincident neural and muscular lesions."

In our case, there were minor changes in the motor neurones of the oculomotor, trochlear, and abducens nuclei—the cells were smaller, rounder, and less polygonal and contained pigment and vacuoles. The cytoplasmic pigment was found in many other neurones in our patient, and we feel that this represents the usual cytoplasmic pigment inclusions noted in older people. The pathologic importance of single vacuoles with the other elements of a nerve cell intact has been severely questioned.[34] The change in the size and contour of the motoneurones might well represent a change subsequent to loss of muscle fibers at the end of these nerves. Of more uncertainty are the definite chromatolytic changes noted in one masticator nucleus and in the abducens nuclei. We wondered whether these might not have resulted from some effect of the cerebral tumor and the associated increased intracranial pressure.

Comparison with Other Cases with Autopsy.—There are in the literature three cases of this disease in which autopsy was performed. None of these has been studied as extensively as our case (Table). Langdon and Cadwalader § and Jedlowski [4] concluded from their studies that the disease process was neuronal. We agree with Kiloh and Nevin [1] that such a conclusion was hardly justified by their histologic findings; and this opinion would seem to be further strengthened by their failure to study thoroughly the whole neuromuscular unit. While Beckett and Netsky [6] concluded that the disease process in their case was a form of muscular dystrophy, it could be said that such a view would have been on stronger ground if they, too, had studied all portions of the neuromuscular unit in their case. Even the ocular muscle biopsies reported by Kiloh and Nevin [1] offered no information as to the condition of the intramuscular nerve fibers and nerve endings. Yet, despite these shortcomings and the differences in interpretation, it would seem that the evidence accumulated to date indicates that chronic progressive external ophthalmoplegia may quite rightfully be considered an "ocular myopathy," as suggested by Kiloh and Nevin.[1]

Certain Autonomic Theories.—The etiology of muscular dystrophy remains unknown. Theories concerned with etiology have been abundant. Of the many unsatisfying theories, not one has been as intriguing as the one formulated by a group of Japanese investigators. They have insisted that the trophic state of voluntary muscle is dependent on the autonomic nerve fibers to such muscle. In a series of papers, they presented evidence that muscle changes resembling those of progressive muscular dystrophy could be produced by proper autonomic extirpations. Thus, they provided a technique for producing an experimental form of muscular dystrophy.

§ References 2 and 3.

Our attention was drawn especially to an article by Sunaga,[35] who claimed to have produced changes in the extraocular muscles of dogs by various autonomic extirpations. For instance, removal of a ciliary ganglion produced changes in the extraocular muscles on the side of operation which resembled those seen in progressive muscular dystrophy; such changes were minor in degree 2 weeks after the extirpation and were definite on the 23d postoperative day. The pathologic changes he described consisted in a marked difference in the thickness of the muscle fibers, a rounding of the muscle fibers, the appearance of very large muscle fibers, vacuolation and splitting of muscle fibers, an increase in muscle nuclei, an appearance of central nuclei, and an increase in the interstitial connective tissue. Removal of the cervical sympathetic chain resulted in similar, but much less severe, changes in the ipsilateral extraocular muscles. The atrophy of the extraocular muscles, which resulted from the destruction of the cerebrospinal motor innervation of these muscles, was delayed significantly if the ciliary ganglia were intact.

We studied the ciliary ganglia of our patient and found no consistent or significant ganglionic cell changes. It seemed to us that the extensive pathologic changes in the eyeball muscles in our case were such that they could certainly not be accounted for by the meager alterations in the neurones in the ciliary ganglia.

SUMMARY

A white man presented signs and symptoms of bilateral ptosis and practically complete paralysis of the extraocular muscles. The onset had been more than 35 years before his death, at the age of 63.

Neuropathologic studies of the oculomotor, trochlear, and abducens nuclei and nerves of this patient revealed insignificant changes. Studies of the superior rectus, superior oblique, and lateral rectus muscles showed marked destruction of muscle fibers and overgrowth of fat and connective tissue—changes compatible with those seen in muscular dystrophy. Intramuscular nerve fibers were abundant, and motor end-plates were identified in the degenerated extraocular muscles.

It was felt that the bulk of evidence favored the opinion that chronic progressive external ophthalmoplegia is a form of muscular dystrophy.

Miss Elsie Toms and Mrs. Chan-Nao Liu prepared the histologic material, and Mr. Laurie W. Winning made the photomicrographs.

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Pathologic Findings

Author	Year	Sex	Age at Death, Yr.	History and Clinical Findings	Nuclei of Brain Stem	Nerve Fibers—Intra-Axial and Extra-Axial	Extraocular Muscles	Intramuscular Nerve Fibers and Nerve Endings
Langdon and Cadwalader [*]	1928	F	84	Onset of ptosis on right at age of 43; left ptosis began soon thereafter; nine years before death almost total external ophthalmoplegia; very nearly complete loss of all extraocular muscular power; pupils equal and reacting to light; other cranial nerves intact; no other reflex or motor changes	III, IV, and VI nuclei: very slight chromatolysis; cells slightly diminished in number; variation in size of cells—one-half to one-third smaller in diameter than normal nuclei of young adult as control	Intra-axial: Smaller in diameter and less numerous Extra-axial: Smaller in diameter	Not examined	Not examined
Jedlowski [4]	1943	F	25	Onset of ptosis on right at age of 19; onset of left ptosis at the age of 24; development of bilateral external ophthalmoplegia at age of 24; pupils equal and reacting well to light and in accommodation-convergence	III, IV, and VI nuclei showed changes; cells reduced in number, deformed, shrunken; nuclei displaced to periphery; Nissl material powdery or in homogeneous mass; few remaining normal cells; nuclei of Edinger-Westphal and of Perlia intact	Intra-axial portions unchanged	Right superior rectus and left internal rectus muscles showed "atrophy of a secondary type, not of marked degree"	Not examined
Beckett and Netsky [6]	1953	M	68	Onset of ptosis at 20; sometime thereafter difficulty in moving eyeballs began, with gradual progression. Examination: Pronounced bilateral ptosis; small, slightly irregular pupils, which reacted poorly to light; eyeballs could not be moved	III and VI nuclei studied; ganglion cells "normal in number and appearance"	Not described	Replacement by fatty tissue; focal, but widespread, increase in sarcolemmal nuclei; focal phagocytosis of muscle fibers; extensive loss of cross striations	Not described

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ISONIAZID IN TREATMENT OF THE CHRONIC SCHIZOPHRENIC PATIENT

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SINCE the demonstration of the antituberculosis activity in experimental animals and in vitro of the hydrazine derivatives of isonicotinic acid* and their therapeutic use in human tuberculosis,[4] both the Committee on Therapy of the American Trudeau Society[5] and the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council of Great Britain[6] have mentioned the occurrence of adverse mental reactions as one of the occasional toxic effects. An early report noted intensified color imagery.[7] Similar color intoxication has been observed preceding the formed visual hallucinations in mescaline† and *d*-lysergic acid[10] psychosis. The usual progression, however, is from irritability to a toxic delirium, with confusion, disorientation, hallucinations, and delusions.‡ In one of the two cases of peripheral neuropathy described by Jones and Jones[13] an associated pellagra-like dermatitis and mental confusion followed isoniazid therapy. McConnell and Cheetham[14] report acute pellagra during isoniazid therapy, with dermatitis, diarrhea, and a catatonic schizophrenic reaction, manifested by marked thought blocking, incongruity between emotion and stimulus, ambivalence, sudden impulsive movements, and, possibly, hallucinations. The syndrome cleared when isoniazid was stopped and vitamin therapy, notably nicotinic acid, was given. One of Hunter's[15] patients on isoniazid showed a confusional psychotic reaction with memory loss, disorientation, persecutory delusions, auditory and visual hallucinations, apathy, and bizarre behavior. Psychological studies confirmed the clinical impression of residual organic cerebral damage suggestive of a Korsakoff psychosis.

Isolated psychotic reactions from isoniazid and iproniazid (1-isonicotinyl-2-isopropylhydrazine) have been reported by a few of the 56 hospitals contributing their findings to the Quarterly Progress Reports of the Veterans Administration-Army-Navy Study on the Chemotherapy of Tuberculosis.§ At the VA Hospital, Houston, Texas, three patients being treated with isoniazid showed a transitory mental confusion; another, an elderly person with pulmonary insufficiency and mild respiratory acidosis, developed a toxic psychosis, which subsided when the drug was discontinued.‖ Two of the 80 patients receiving isoniazid at the VA

From the Veterans Administration Hospital.

* References 1, 2, and 3.

† References 8 and 9.

‡ References 11 and 12.

§ References 16, 17, and 22.

‖ Reference 16. Veterans Administration Hospital, Houston, Texas: Personal communication to the authors.

Hospital, Walla Walla, Wash. showed hallucinatory psychotic reactions.[17] The VA Hospital, New Orleans, reports one instance of psychotic behavior in 60 patients with tuberculosis treated with isoniazid alone or in combination with streptomycin (SM) and *p*-aminosalicylic acid (PAS).¶ This patient became depressed, showed emotional instability, complained of sensations of unreality and of paresthesias involving the thighs and pubic region, and exhibited illogical thought content and paranoid trends. All evidence of abnormal behavior subsided immediately on withdrawal of isoniazid and PAS and did not recur. One patient at the VA Hospital, Brooklyn, while showing no adverse reaction to isoniazid, developed a psychosis with persecutory delusions and auditory and visual hallucinations when iproniazid was substituted. The mental picture cleared after the discontinuance of iproniazid and readministration of isoniazid.# One patient out of 50 on isoniazid therapy at the Rush Hospital, Philadelphia, showed a toxic psychotic reaction, with delirium and hallucinations. The psychosis disappeared after the drug was stopped and did not recur when the drug was readministered. Three patients out of 25 developed a toxic psychosis during iproniazid therapy.* At Trudeau Sanatorium there were no such reactions in 35 patients on isoniazid alone or in combination with SM or PAS. One agitated paranoid reaction of a psychotic degree was noted in the 42 patients receiving iproniazid alone or in combination with other drugs. Mention, however, is made of a considerable number of mental changes of various sorts occurring in approximately 30% of the iproniazid group, ranging from nightmares through mild personality changes to the one psychotic reaction. Seven of the 42 in the group required termination of treatment because of these effects.† O'Connor and Howlett,[18] while noting no psychotic manifestations in 59 patients receiving isoniazid, did observe such an effect in 3 of the 27 taking iproniazid. One showed a manic and the other two showed paranoid reactions. They also report 3 cases of psychoses in 17 patients receiving iproniazid at two other sanatoria. The greater frequency of psychoses from iproniazid was also pointed out by Jenkins and associates,[19] who noted 8 toxic psychotic reactions in 30 patients receiving iproniazid, as compared with 1 in 31 patients taking isoniazid.

Selikoff, Robitzek, and Ornstein [20] stress that with isoniazid and iproniazid, serious central nervous system side-effects are commoner in persons who have unstable personalities, a history of previous psychotic episodes, or a history of previous convulsive disorders. Instances of aggravation of overt psychoses or activation of latent ones have been reported during the administration of these drugs. Hypothesizing isoniazid as an animal protein factor and so using it in the treatment of adaptive diseases, Barnard [21] noted a confusional psychosis when the drug was given to one of his patients. However, this type of psychotic reaction had occurred previously in this patient in response to cortisone and oxytetracycline (Terramycin) treatments. One patient at the VA Hospital, New York, who had developed hypomania postoperatively, reacted with depression and confusion after isoniazid was administered.

¶ Reference 17. Veterans Administration Hospital, New Orleans: Personal communication to the authors.

Reference 17. Veterans Administration Hospital, Brooklyn: Personal communication to the authors.

* Ralph, N.: Personal communication to the authors.

† Coates, E. O., Jr.: Personal communication to the authors.

However, in spite of the discontinuance of isoniazid, the psychosis went on to become an unclassified schizophrenia. The question was raised whether the isoniazid had aggravated an existing psychosis or whether the psychosis would have progressed spontaneously and so was not influenced by the drug.‡ Strassman § cites one case of a schizoid patient who developed an acute paranoid schizophrenic episode on administration of isoniazid, which remitted only partially when the medication was discontinued. In a preliminary report on isoniazid, Heilmeyer and associates [23] describe a case of an acute schizophrenic episode with catatonic features. Since the patient had a "tainted" background, no conclusion is drawn as to the causal relation of the psychosis to the drug. Of the seven psychotic tuberculous patients transferred over a period of six months from the VA Hospital, Kerrville, Texas, to the VA Hospital, Waco, Texas, because of unmanageability, six had been receiving isoniazid. Only three, however, had symptoms somewhat suggestive of toxic delirium, and it was the psychiatric opinion that isoniazid did not bring about the acute psychotic episodes.‖ One patient at the VA Hospital, Richmond, Va., who had had an acute psychotic episode three years previously, probably on an alcoholic basis, became excited, disturbed, and out of contact while receiving isoniazid with SM and PAS. However, since the psychotic episodes were recurrent with or without the drug, a causative relationship is questionable.¶

While the various reports would seem to indicate, on the whole, detrimental psychiatric effects of a toxic and transitory nature with the isonicotinic acid derivatives, Flaherty [24] mentions a case of an alcoholic whose toxic confusional psychosis cleared completely while she was receiving isoniazid for pulmonary tuberculosis. In this case, however, there was a marked improvement in the tuberculous process, so that the mental improvement may have been a reflection, in great part, of her general physical state.

Krieser and associates [25] report mental improvement in 21 of 48 male and female tuberculous psychotics given isoniazid, 2 mg. per kilogram of body weight, daily for 10 days, and 4 mg. per kilogram of body weight, daily for the remainder of a 90-day period. Eighteen of the 35 schizophrenics in the group showed improvement. Criteria included "such changes as spontaneous activation in catatonics, even though this might be of a belligerent nature." It was felt that the improvement was "more than a temporary feeling of euphoria or increased sense of well-being," and, in some cases, it appeared to "represent a renewed contact with reality in patients who have been withdrawn and hallucinated for a prolonged period." The mental changes were not felt to be due to suggestion or increased attention, since the patients had received extensive medical treatment previously. Furthermore, according to the authors, after the drug was stopped, the majority did not relapse.# These findings were unexpected in the course of the investigation of possible toxic effects. Appar-

‡ Reference 22. Veterans Administration Hospital, Bronx: Personal communication to the authors.

§ Strassman, H. D.: Personal communication to the authors.

‖ Reference 22. Veterans Administration Hospital, Waco, Texas: Personal communication to the authors.

¶ Reference 17. Veterans Administration Hospital, Richmond, Va.: Personal communication to the authors.

Krieser, A. E.: Personal communication to the authors.

ently, only gross subjective evaluations were made, and no control population was utilized. The report was a cautious one, and these effects were mentioned simply to stimulate further research.

Seventeen male tuberculous psychotics, 12 of whom were chronic schizophrenics, received isoniazid, 9 to 10 mg. per kilogram of body weight, daily for 90 days at the Norristown (Pa.) State Hospital. Six of the 12 schizophrenics showed "a definite, though mild, behavior improvement." The patients partially regressed when isoniazid was discontinued.[26] Fourteen psychotics with tuberculosis were given isoniazid alone, 5 mg. per kilogram of body weight, daily, at the VA Hospital, Montrose, N. Y. There were 11 schizophrenics in the group, 4 of whom received the drug for one year, 2 for nine months, and 5 for five months. Seven of the 11 became more agitated during the first few months of treatment, with 3 requiring electric shock. It was believed that the disturbed state was not due to the drug, but was the result of the numerous laboratory examinations, since the agitation subsided as the intervals between the procedures lengthened and did not recur when isoniazid was given again in combination with other drugs.* The others showed no change. At the VA Hospital, Coatesville, Pa., nine tuberculous male chronic schizophrenics receiving isoniazid, 300 mg. daily, were carefully studied by the psychiatric staff for one year, without any noticeable change in their mental status being seen. MacKinnon and associates[27] report the use of isoniazid, 150 to 600 mg. daily, in 20 early and 20 chronic schizophrenics, a control population being administered a placebo. The result showed that in the early cases a small number had an increase of symptoms and a small number of patients had a diminution of symptoms. Marshall† at Friends Hospital, Philadelphia, studied the effect of isoniazid given in a dosage of 8 mg. per kilogram of body weight daily for periods varying from four weeks to four months, on 10 male and 4 female chronic schizophrenic patients. Four showed slight but temporary improvement in an increase of psychomotor activity, similar to that seen with the sympathomimetic drugs. One patient, previously nondisturbed, became violent while on the drug.

Although most of the reported cases are those showing an adverse effect upon the mental state from the isonicotinic acid derivatives, the fact that there have been contradictory results in the treatment of the chronic schizophrenic patient led us to the present study.

PROCEDURE

Sixty chronic schizophrenic patients from the continued-treatment service of the VA Administration Hospital, Coatesville, Pa., were selected for this study and randomly assigned to either the experimental or the control group. Each group included 30 subjects. There was no question of diagnosis in any of the cases, with complete diagnostic agreement by the hospital psychiatric staff in each case. The two groups contained approximately equal numbers of patients representing the various schizophrenic subtypes. All subjects were housed on the same ward and had been participating in the same hospital program of "total push" and hospital industries prior to the study. This program was continued throughout the study. The mean age of the experimental group was 38.57 years, with a standard deviation of 9.67 years. The mean age and standard deviation of the control group were 34.90 and 3.90 years. The mean duration of illness of the experimental group was 13.70 years, and the standard deviation, 8.17 years, while the mean of

* Reference 16. Veterans Administration Hospital, Montrose, N. Y.: Personal communication to the authors.

† Marshall, B.: Personal communication to the authors.

the control group was 9.67 years and the standard deviation 4.52 years. Practically all subjects in both groups had received previous deep insulin and/or electric shock therapy. There were no significant differences between the groups in any of the above variables.

In order to evaluate the variable of drug dosage, 15 of the experimental group were administered 50 mg. of isoniazid t. i. d. and the other 15 were administered 100 mg. t. i. d. for 90 days. Subjects of the experimental group were randomly assigned to these dosage groups. The control group was administered a placebo, given with the same frequency and duration as the experimental drug. Ward procedure was identical for all patients.

The behavior of all 60 subjects was rated before the study with a modification of the Gardner Behavior Chart 28. The two groups were comparable in severity of illness in terms of this rating scale. All subjects were then rated weekly throughout the study, at the termination of treatment, and two months after cessation of treatment for a total of 14 ratings per subject for each of the three observers. Behavior ratings were effected by the ward charge nurse, by the ward charge aide, and by the chief of hospital industries, all of whom had been working closely with these patients for at least two years prior to the study. The three raters did not know at any time to which group each subject was assigned. Each observer, rating independently of the others, observed the patients at different periods of the day, thereby affording observations over a 24-hour period and permitting them to detect even minor fluctuations in behavior.

Neurological and psychiatric examinations were performed on all subjects by one of us (I. F. B.) before, twice during the study, at its termination, and two months after cessation of treatment. These examinations and evaluations were also independent of the other ratings and examinations.

Laboratory studies of the isoniazid group included C.B.C., BUN, urinalysis, and evaluation of liver function, using the cephalin flocculation, thymol turbidity, and sulfobromophthalein U. S. P. (Bromsulphalein) excretion tests before, at monthly intervals during, and after the study. EEG's were taken on the subjects before, during, and after treatment. Eosinophile counts on fasting normal blood specimens were taken for the experimental and control groups before and after treatment.

Psychological studies consisted of select subtests of the Wechsler-Bellevue Adult Intelligence Scale, Form I; Rorschach Psychodiagnostics, Human Figure Drawings, and a newly devised test which considers a subject's conceptualization of the internal body organization. The battery of psychological tests was administered to all subjects before and after the course of treatment.

FINDINGS

1. *Laboratory Data.*—Urinary constituents and blood urea nitrogen remained normal in the 30 patients of the experimental group. In 5 of the 30 there was a positive cephalin flocculation reading during the study, not associated, however, with an abnormal thymol turbidity value or sulfobromophthalein excretion rate and disappearing shortly. Selikoff, Robitzek, and Ornstein [20] mention several positive cephalin flocculation tests in patients with systemic toxicity, and Lattimer [29] notes weekly progressive elevation of cephalin flocculation and sulfobromophthalein tests. Elmendorf and associates,[30] and Cooper, Eisenberg, and Weiss [26] have detected no disturbance in hepatic function in using these tests alone or in combination. Pitts and associates [31] observed a transient sulfobromophthalein retention in 21% and a passing abnormal cephalin flocculation test in 4%.

Table 1 reveals the means and standard deviations for the eosinophile count in the experimental and control groups before and after treatment. The analysis of variance reveals no significant change between pretreatment and post-treatment counts either within each of the groups or among the various groups. There is also no significant change in the variability of the count. The differences can be attributed to chance factors alone. Isoniazid has no significant effect on the eosinophile count when administered either as 50 or as 100 mg. t.i.d. when the counts were

taken before and after the 90-day period of treatment. When the pretreatment eosinophile counts of all 60 patients are compared with the counts after treatment, no significant change is noted.

To observe the daily effect of the drug, fasting, four-hour, and six-hour eosinophile counts were taken on 10 randomly selected patients of the experimental group at the end of the second week of the study (five received 50 mg. t.i.d., and five received 100 mg. t.i.d.). Fasting counts at this point did not differ significantly from the prestudy readings. Differences in the fasting, four-hour, and six-hour readings were not greater than the expected variation in a group of healthy normals.[32] There was no significant difference between the 50 and the 100 mg. groups. The less reliable eosinophile determination, using the differential smear, which was not run concomitantly with the chamber eosinophile counts, showed that 3 of the 30 subjects in the experimental group had a 5 to 10% transient eosinophilia. This is in agreement with the findings of other investigators.‡

TABLE 1.—*Means and Standard Deviations of Eosinophile Count for Experimental and Control Groups Before and After Treatment*

		Experimental Groups			Control Group	
		50 Mg. INH t.i.d. N-15	100 Mg. INH t.i.d. N-15	Total	N-30	Variance* Between Methods
Before treatment	Mean.....	349.87	197.87	273.87	291.93	.....
	S. D.....	252.05	79.64	196.85	161.88	.....
After treatment	Mean.....	282.27	191.20	236.73	280.77	.....
	S. D.....	159.92	100.13	137.16	153.24	F 0.826 Differences, pre- and post-treatment

* *F* value is not significant at the 0.05 level of confidence.

Nine of the 30 subjects of the experimental group were sufficiently cooperative to permit waking and sleeping EEG tracings to be obtained. Comparison of pretreatment and post-treatment tracings revealed no significant differences. However, the waking records obtained during the drug administration revealed a rather low amplitude and fast activity of 20 to 30 per second in six of the nine subjects. This was not observed in the sleeping records and is similar to that seen in persons taking barbiturates or other sedatives. It is interesting to note that this same pattern was found in four of six cooperative tuberculous schizophrenic patients receiving isoniazid.§

2. *Clinical Side-Effects.*—There were no subjective complaints while the drug was being administered. One patient developed an erythema multiforme of both hands, which was thought by the dermatologist to be on an allergic or a toxic basis. It did not recur when the isoniazid was readministered. Dermatitis has been noted as one of the side-reactions.‖ Five of the 30 patients receiving the drug developed a temporary hyperreflexia, which has been frequently reported in the literature.¶

3. *Psychiatric Evaluations.*—Psychiatric examinations showed very slight, but definite, clinical improvement in four of the study group and one of the control

‡ References 20, 26, 30, and 31.

§ The EEG tracings were interpreted by Dr. Francis P. Knight, Chief, EEG Service, VA Hospital, Coatesville, Pa.

‖ References 5 and 6.

¶ References 5, 6, 20, 33, 34, 35, and 36.

group. This consisted of an increased spontaneity, with the patient becoming more communicative, friendly, and less apprehensive and tense in the interview situation. This improvement, however, was only transitory and occurred in patients who had been observed previously to have such fluctuations in their mental status.

4. *Modified Gardner Behavior Chart.*—This is an instrument by which observers can rate a subject's personality and behavior along various dimensions, such as appearance, sleep, appetite, sociability, activity control, assaultiveness, destructiveness, cooperation, and work capacity. The scale was modified by us to include reactions to hallucinations and delusions and to permit more refined ratings of inactivity and mood.

Table 2 indicates no significant differences between the ratings for the experimental group and those for the control group prior to, six weeks after the beginning of treatment, at the termination of treatment, and two months thereafter. There is no reason to believe that additional ratings, after increasing the time, would lead to significant behavior changes. The differences in methods and in the four successive

TABLE 2.—*Means, Standard Deviations, and F Values of Modified Gardner Behavior Chart for Experimental and Control Groups*

		50 Mg. INH t.i.d. N-15	100 Mg. INH t.i.d. N-15	Total	N-30	Variance* Between Methods	Variance Between Ratings	Variance Interaction Ratings and Method
Pretreatment	Mean	2.65	2.62	2.64	2.60	....	....	....
	S. D.	0.44	0.34	0.38	0.23	....	....	....
During treatment	Mean	2.56	2.60	2.58	2.56	....	....	....
	S. D.	0.40	0.37	0.37	0.25	....	....	....
Post-treatment 1	Mean	2.48	2.64	2.56	2.57	....	....	....
	S. D.	0.42	0.40	0.41	0.26	....	....	....
Post-treatment 2	Mean	2.79	2.90	2.85	2.80	....	....	....
	S. D.	0.45	0.34	0.39	0.27	*F* 0.16	*F* 1.00	*F* 1.05

*F values are not significant at the 0.05 level of confidence.

ratings, and the interaction between method and successive ratings can all be accounted for in terms of random samplings from a common population. Neither dosage of isoniazid was effective in bringing about significant behavior changes.

5. *Psychological Data.*—An attempt was made to test each subject with a complete psychological battery before and after treatment. However, as was expected, various persons in both groups were unable to or refused to comply with the test directions. Attitude toward test procedures and ability and willingness to comply with directions may be considered important indices of adjustment. On each of the following psychological tests, therefore, a separate analysis of these refusals was made to determine whether subjects receiving isoniazid may have become more accessible and cooperative to test demands. There was no significant difference between experimental and control groups in this variable, nor were there significant differences between the two isoniazid groups.

Table 3 reveals the means, standard deviations, and variances (F values) between the groups, before and after treatment, for the psychological tests.

A. Wechsler-Bellevue Adult Intelligence Scale, Form I: Table 3 *A* indicates no significant difference in intellectual efficiency among the groups at the onset of the study and practically no change in intellectual functioning within any of the groups after the three-month period of study, regardless of treatment. The same

bizarre, confused thinking and attention disturbance characterized the behavior of both the experimental and the control group both before and after treatment. Isoniazid with either dosage had no effect upon intellectual efficiency. The mean I. Q.'s listed in Table 3 are based upon the estimated full-scale I. Q. of the individual subjects of each group in terms of the subject's age. Those subjects who did not comply with all six of the subtests are not included. This Table also includes the mean differences and standard deviations of these differences for each of the

TABLE 3.—*Means, Standard Deviations, and F Values of Psychological Tests for Experimental and Control Groups*

	Experimental Groups						Control Group		
	50 Mg. INH t.i.d.	N	100 Mg. INH t.i.d.	N	Total Group	N		N	Variance* Between Methods
A. Wechsler-Bellevue Adult Intelligence Scale Form I									
1. Pretreatment									
Weighted scores	41.50	10	43.80	10	42.65	20	35.58	19	*F* 0.73
6 subtests	17.53	..	19.58	..	19.61	..	17.55	..	.....
Mean I. Q.	88.70	..	87.60	..	88.15	..	80.00	..	.....
2. Subtest Differences in Pretreatment and Post-Treatment Scores									
Total	−3.12	8	+2.33	9	−0.235	17	−0.45	20	*F* 0.91
6 subtests	16.89	..	3.86	..	11.12	..	4.71	..	.....
Information	−1.60	10	+0.30	10	−0.65	20	+0.15	20	*F* 2.45
	2.65	..	1.32	..	2.06	..	1.56	..	.....
Digit span	−0.82	11	−0.67	9	−0.75	20	+0.05	21	*F* 0.39
	4.42	..	2.59	..	3.45	..	2.25	..	.....
Similarities	−1.10	10	+0.22	9	−0.47	19	+0.50	22	*F* 2.08
	3.27	..	2.04	..	2.63	..	1.50	..	.....
Vocabulary	−0.89	9	0.00	8	−0.47	17	−0.32	22	*F* 0.38
	2.56	..	2.43	..	2.32	..	2.01	..	.....
Picture completion	0.00	10	+0.44	9	+0.21	19	−0.14	22	*F* 0.15
	3.73	..	2.96	..	3.12	..	2.21	..	.....
Block design	−0.30	10	+1.12	8	+0.33	18	0.00	22	*F* 1.50
	2.17	..	2.76	..	2.35	..	1.38	..	.....
B. Internal Body Organization Test									
Pretreatment	7.63	11	8.28	9	7.92	20	7.80	20	*F* 1.96
	2.31	..	2.43	..	2.36	..	2.27	..	.....
Post-treatment	7.31	8	7.50	8	7.40	16	7.15	23	*F* 0.26
	1.85	..	2.41	..	2.09	..	2.93	..	.....
C. Human Figure Drawing									
Comparative weighted ratings.	17.30	5	16.50	8	16.80	13	17.40	17	*F* 0.36
	1.33	..	3.64	..	3.25	..	8.68	..	.....
D. Rorschach Test									
Comparative weighted ratings.	20.37	8	20.14	7	20.27	15	19.42	19	*F* 0.12
	5.07	..	4.97	..	5.02	..	3.90	..	.....

* *F* values are not significant at the 0.05 level of confidence.

groups on the individual subtests administered. Since various subjects refused various of the subtests, the N values vary from subtest to subtest.

B. Internal Body Organization: This test is part of a battery devised at this hospital to evaluate a patient's awareness of his internal body organization. The subject is asked to name and draw the internal organs on a mimeographed figure of a person. He is then questioned concerning the organs of most and least importance to him and why. Performance is scored in regard to number of organs drawn, size, correct placement, relationship to each other, bizarre features, and importance. The lower the score, the more adequate is the individual's conceptualization of his internal body. The test is essentially an extension of suggestions found in the writings of Schilder [37] and is to be reported in detail in a later paper.

Table 3 *B* indicates no significant differences among the initial scores of the groups and no significant changes on this test in any of the groups as a result of treatment.

C. Human Figure Drawing: In this test the subject is presented with an 8 by 10½ in. blank sheet of paper and asked "to draw a person." The resulting productions may be considered in terms of the subject's ability and willingness to comply with instructions and as important projective material related to ego organization and other dimensions of personality. The pretreatment and post-treatment drawings of each subject were compared by three staff psychologists to determine significant changes on nine rating items. A significantly high interjudge reliability was obtained on the four following items: "ability to comply with the task," "changes in awareness of self and others," "activity of the figures, judged from overt bodily movement in the drawings," and "degree of significant clinical change in overt behavior." (Interjudge reliability coefficients, uncorrected for coarseness of grouping, on three items ranged from 0.494 to 0.791. They were significant at the 0.05 level of confidence. There was 100% agreement among the judges on the item dealing with the subject's ability to comply with the task.) The three judges rated independently of each other and were not aware of the group membership of any of the subjects. A numerical weight was assigned to the various degrees of change—less, same, and more. By summing the weights for each pair of drawings compared, an over-all quantitative score representing total degree of change between pretreatment and post-treatment drawings was obtained for each subject in the various groups. The mean weighted scores and score variance for each group are shown in Table 3 C. Analysis of variance indicates no significant difference among the groups in direction and degree of change between pretreatment and post-treatment drawings.

D. Rorschach Psychodiagnostics: The usual test procedure was followed in administration of this test, except that "testing the limits" was not employed. Pretreatment and post-treatment records of each subject were compared in terms of (1) individual and combined scoring variables, and (2) independent comparisons by three judges of each pair of pretreatment and post-treatment protocols to determine degree and direction of changes along four dimensions of personality.

A large number of scoring variables singly and in combination were studied. These included number of responses; W, D, d, Dd percentages; reaction time (total, chromatic, achromatic); movement; shading; F, F+, R+ percentages; achromatic and color responses; movement-color relationships; responsivity to last three cards; popular and original responses; content; bizarreness in thinking, and card rejections.

Of the four items on which the judges compared the pretreatment and post-treatment Rorschach protocols of each subject, significantly high interjudge reliability coefficients existed on two items—"adequacy of perception" and "degree of significant clinical change in overt behavior." (Coefficients ranged from 0.394 to 0.837, uncorrected for coarseness of grouping, and were significant at the 0.05 level of confidence.) As in the Draw a Person test, numerical weights assigned to the various degrees of change—markedly worse, slightly worse, no change, slightly better, much better—were totaled for each subject to quantify the direction and amount of change. Neither method of comparison showed any significant differences among the groups in direction and degree of change between the pretreatment and the post-treatment protocols. Table 3 indicates the mean weighted scores and score variances for each group.

SUMMARY

In order to determine the usefulness of isoniazid in the treatment of the chronic schizophrenic patient, the present investigation was undertaken.

Sixty chronic schizophrenic patients of comparable age, and duration and severity of illness were randomly assigned to two groups, one of which received isoniazid for 90 days and the other received a placebo for the same period. Subjects of the experimental group were randomly assigned to two groups, one of which received 50 mg. of isoniazid t.i.d., and the other 100 mg. t.i.d. Ward procedure was identical for all patients. The behavior of all subjects was rated with a modification of the Gardner Behavior Chart before, at weekly intervals during, at the termination of treatment, and two months after cessation of treatment by three independent observers—the ward charge nurse, the ward charge aide, and the chief of hospital industries. Studies on the isoniazid group included C. B. C., BUN, urinalysis, evaluation of liver function, and electroencephalograms before, during, and after treatment. Eosinophile counts were taken, and psychiatric and neurological examinations were performed on all subjects before, during, and after treatment. Psychological studies consisted of select subtests of the Wechsler-Bellevue Adult Intelligence Scale Form I, Rorschach Psychodiagnostics, Human Figure Drawing, and a newly devised test which considers an individual's conceptualization of the internal body organization.

FINDINGS

1. Laboratory, clinical, and psychiatric examinations; behavior ratings, and psychological test data reveal no significant differences between the experimental and the control group as a result of isoniazid when administered in doses of either 50 or 100 mg. t.i.d. for 90 days. There is no reason to believe that an increased period of medication on these dosages would lead to significant changes.

2. Laboratory studies of the experimental group revealed positive cephalin flocculation readings in 5 of the 30 subjects, but this result was not associated with disturbance in other liver function studies. Furthermore, the deviant readings returned to normal after cessation of treatment. Isoniazid in either dosage had no significant effect on the eosinophile count, nor were there significant differences in the fasting, four-hour, and six-hour readings from the expected variation in a group of healthy normals.

3. Nine of the 30 subjects of the experimental group were sufficiently cooperative to obtain waking and sleeping electroencephalographic tracings. Comparison of pretreatment and post-treatment EEG tracings revealed no significant differences. However, the waking records obtained during the drug administration revealed a rather low amplitude and fast activity of 20 to 30 per second in six of the nine cases. This was not observed in the sleeping records and is similar to that seen in patients taking barbiturates or other sedatives. It is interesting to note that this same pattern was found in four of six cooperative tuberculous schizophrenic patients receiving isoniazid.

4. Clinical side-effects were few, transitory, and of minor importance, consisting of hyperreflexia in five cases and possible erythema multiforme in one case.

5. The improvement noted by psychiatric evaluation in four of the study group and one of the control group may be disregarded, since it was only transitory and occurred in persons who had been observed previously to have fluctuations in their mental status.

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PATHOLOGICAL CHANGES IN NEURONS, NEUROGLIA, AND BLOOD-BRAIN BARRIER INDUCED BY X-IRRADIATION OF HEADS OF MONKEYS

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LOS ANGELES

IN COMPARISON with the severe changes seen in many tissues, reports concerning the effects of ionizing radiation on the adult central nervous system have usually indicated a relative radioresistance on the part of the brain.* This observation is supported by experiments suggesting that sensitivity to irradiation depends in part on the rate of synthesis of nucleic acids, the lymphocyte and the maturing neuroblast appearing more radiosensitive than the adult neuron.[5] Despite these general statements, reports from both clinical † and experimental sources ‡ reveal that irradiation can produce extensive neuronal pathology and overt neurological disorders. Of key interest here has been the question of the relative importance of direct and indirect neuronal injury: direct by primary alteration of nerve cells, and indirect from changes secondary to alterations in neuroglia or the blood-brain barrier. In this connection, primary impairment of neurons, of neuroglia, and of the vascular system has each been cited as the principal cause of the neurological abnormalities observed.

As evidenced by edema and vascular fragility, nonspecific permeability changes may occur in the central nervous system after irradiation.§ The concept of a selective barrier between the blood and the brain in the normal animal has generally been accepted, since it has been shown that certain negatively charged substances circulating in the blood are uniquely incapable of entering the nerve tissue. This phenomenon can be demonstrated grossly by intravenous or intraperitoneal injection of certain vitally staining acid aniline dyes, such as trypan blue, and has often been described since Ehrlich's experiments at the end of the last century. In the normal animal, trypan blue so injected stains the tissues of every organ except the central nervous system. The dura mater, choroid plexus, and walls of cerebral vessels stain vitally, as do the neural stalk and the area postrema; but the dye normally does not penetrate the central nervous system proper. Because the passage

This study was aided by a grant from the National Institute of Neurological Diseases and Blindness.

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‡ References 9, 10, and 11.

§ References 10, 11, 12, and 13.

of nutritional solutes between blood and brain may be mediated through those structures comprising the blood-brain barrier, the great functional importance of this barrier is obvious.

The present work on the monkey has utilized permeability to trypan blue as a measure of impairment of the blood-brain barrier resulting from exposure of the

Summary of Data on Animals, with X-Ray Dosage and Time of Death

Monkey No.	Dose, r	Weight, Kg.	Sex	Trypan Blue Injected (TB)	Death, Time After Irradiation
A- 1	6,000	3.2	F	—	48 hr.
A- 2	6,000	2.2	F	—	55 hr.
A- 3	6,000	2.4	F	—	12 days
A- 4	6,000	3.7	F	—	52 hr.
A- 5	6,000	3.3	F	—	36 hr.
A- 6	6,000	2.3	F	—	12 days
A-26	6,000	2.6	M	TB	18 hr.
A-30	6,000	2.8	F	TB	32 hr.
A-31	6,000	3.2	F	TB	16 hr.
A-32	6,000	2.7	F	TB	8 hr.
A-39	6,000	2.8	F	TB	36 hr.
A-33	4,500	3.0	M	TB	10 days *
A-34	4,500	2.5	F	TB	6 hr.
A-35	4,500	2.3	F	TB	21 hr.
A-38	4,500	2.5	F	TB	5 days *
A-40	4,500	2.5	F	TB	34 hr.*
A-11	3,000	2.1	F	—	18 days
A-12	3,000	2.0	F	—	18 days
A-13	3,000	2.1	F	—	21 days *
A-14	3,000	1.7	F	—	17 days
A-15	3,000	2.1	F	—	16 days
A-16	3,000	1.7	F	—	15 days
A-36	3,000	2.6	M	TB	5 days *
A-37	3,000	2.3	F	TB	29 hr.
A-41	3,000	2.5	F	TB	36 hr.*
A-27	2,000	3.1	F	TB	7 days *
A-28	2,000	3.1	F	TB	9 days
A-29	2,000	3.2	F	TB	8 days *
A-17	1,500	2.5	F	—	4 mo.*
A-18	1,500	2.4	F	—	4 mo.
A-19	1,500	3.5	F	—	8 mo.*
A-20	1,500	2.4	F	TB †	6 mo.*
A-21	1,500	3.6	M	TB †	6 mo.*
A-22	1,500	2.5	F	TB †	5 mo.*
A-23	1,500	2.6	F	TB	3 days *
A-24	1,500	3.0	F	TB	12 days *
A-25	1,500	2.1	F	TB	6 days *

* Animals were killed. Other animals were allowed to die or were killed when moribund.
† Trypan blue injected during the week previous to death.

head to ionizing radiation and has correlated this impairment with the pathology of neuroglial and neuronal elements.

METHODS

Thirty-seven monkeys (Macaca mulatta), weighing between 1.7 and 3.7 kg., were used. The head only of each animal was exposed to a single dose of x-rays from a 250-kvp G. E. Maximar unit. The half-value layer for filtration of 0.5 mm. Cu and 1.0 mm. Al at a focal midcranial distance of 35 cm. was 1.4 mm. Cu. The dosage rate was 118 r a minute, as measured by a Victoreen thimble chamber in the center of a cylindrical Masonite phantom with a radial thickness of 4 cm. The center of the phantom was also 35 cm. from the focal point.

Eleven animals received 6,000 r; five, 4,500 r; nine, 3,000 r; three, 2,000 r, and nine, 1,500 r (Table). The body was shielded by placing a ⅛ in. lead cylinder and cone around the animal.[14] The radiation in the shielded space was about 0.5% of that in the unshielded area. In an attempt to equalize exposure, the animal was rotated at a rate of 1 rpm.

Intraperitoneal injections of 1% trypan blue (5 cc. per kilogram) were administered to 19 of the monkeys for three days prior to irradiation and daily up to a week thereafter. Three previously uninjected monkeys also received the dye daily over a period of a week, several months after irradiation. The dye-injected animals were killed at postirradiation intervals of from 6 to 72 hours, 1 to 2 weeks, and 4 to 6 months. Tissue fixation in these animals was by perfusion, first with isotonic saline containing 2.6% acacia,[15] and then with a mixture of 10% formalin, 2% ammonium bromide, 2.6% acacia, and 0.9% saline. The brains were further hardened in formalin or a formalin-ammonium bromide mixture. The remaining animals which had not received the trypan blue injections were allowed to live until they died of the effects of irradiation. The brains

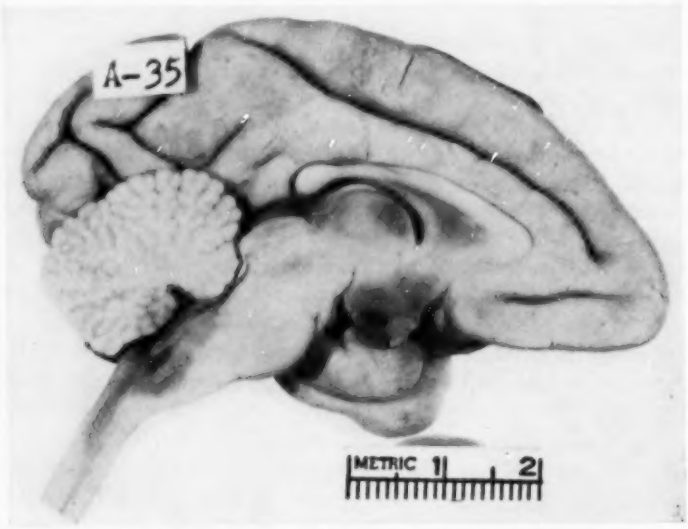

Fig. 1.—Photograph of the median sagittal aspect of the brain of Animal A-35, which received 4,500 r and lived 21 hours after irradiation of the head. Trypan blue has entered the central nervous system in the hypothalamus, optic chiasm, medulla, septum pellucidum, and dorsal thalamus.

of this group were removed and immediately fixed in 10% formalin. Cytological details, however, were studied only in those animals which were killed and fixed by perfusion. The brains of two unirradiated animals, perfused as above, were used as controls.

Paraffin sections, cut at 10 μ, and frozen sections, at 20 μ, were studied, using the buffered thionine method,[16] hematoxylin and eosin, the Weil method for myelin,[17] the Cajal gold chloride-mercury bichloride (gold-sublimate) procedure for astrocytes, and Penfield's combined oligodendroglia and microglia technique.[18]

RESULTS

Observations on Acute Animals.—I. Gross Observations: Of the 19 monkeys injected with trypan blue and killed from 6 hours to 12 days after irradiation, the heads of 5 were exposed to 6,000 r, of 5 to 4,500 r, of 3 to 3,000 r, of 3 to 2,000 r, and of 3 to 1,500 r. Abnormal staining by trypan blue occurred in the brains of 11 of these animals, with the greatest amount of staining in the 6,000 and 4,500 r series. Each of the five animals receiving 6,000 r exhibited the blue coloration,

whereas no dye was seen in the brains of the animals in the 1,500 r series. Two monkeys in each of the 4,500 and 3,000 r groups and one animal receiving 2,000 r also showed trypan blue in the brain.

Although varying degrees of trypan-blue coloration occurred in animals of the different series (Figs. 1 and 2), the sites which stained were strikingly constant. The hypothalamus and optic chiasm, together with the medulla, were oftenest colored, although in occasional animals some dye was seen in the cerebral cortex, thalamus, fornix, septal region, and midbrain. Dye was never observed in the body of the pons, in the cerebellum, or in the basal ganglia (except for the head of the caudate nucleus in one animal). Staining of the hypothalamus and medulla did not occur simultaneously. The dye appeared first in the posterior hypothalamus and then extended into the anterior hypothalamus and optic chiasm, the medulla becoming involved at about the same time as the anterior hypothalamus (Fig. 2).

At autopsy the brains of the animals in the 6,000 and 4,500 r groups appeared very edematous, and there was often a pressure cone at the foramen magnum. Such severe edema was rarely observed grossly after 3,000 r and was not seen after 2,000 and 1,500 r. The ventricles were not observed to be enlarged in these animals.

No large cerebral hemorrhages were seen, although petechiae were occasionally noticed (see below).

II. Microscopic Observations: A. Location of trypan blue. When pieces of the brains showing dye penetration were stained by the Cajal gold chloride-mercury bichloride method, gold was found to be preferentially deposited as particles in areas of trypan-blue coloration, thus allowing microscopic visualization of the distribution of the dye. This was fortunate, since the trypan blue occurred intercellularly in the abnormally colored areas. Ordinary staining procedures involving many changes of solutions removed these dye granules, although intracellular dye, as in the choroid plexus and in phagocytic cells of blood vessel walls, still remained.

Although the blood of the trypan blue-injected animals contained dye both in the plasma and within cells, the cerebrospinal fluid remained untinged, suggesting that the blood-cerebrospinal fluid barrier was intact.

B. Blood vessels. In addition to diffuse cerebral edema and staining of some areas by trypan blue, evidence of a change in composition of the cerebral interstitial fluid was afforded by the inflammatory reaction observed in the irradiated brains. This reaction was severest at the higher dosage levels, occurring only to a slight extent after 1,500 and 2,000 r. It was seen as early as six hours and as late as five days after irradiation. Active inflammation was not found in any brain examined later than one week after irradiation, regardless of the dose received. The inflammatory reaction was a typical one, in which polymorphonuclear leucocytes occurred in large numbers throughout the walls of cerebral vessels, in the Virchow-Robin spaces, and in the interstitial substance (Fig. 3).

In the majority of cases inflammation was widespread through the brain, although it was frequently most intense in the brain stem, especially in the hypothalamus and medulla, to which areas it was restricted in a few animals. It was often observed that the neural stalk and tuberal region, as well as the area postrema, contained many more polymorphonuclear leucocytes than surrounding regions. In the hypothalamus the number of leucocytes in the dorsal portion appeared fewer than in the area adjoining the tuberal region, and likewise, in the medulla, the olivary region showed less inflammation than the dorsal nuclei and the reticular

formation. Regions stained by trypan blue invariably showed an inflammatory reaction. The leucocytes, however, were present in many areas, both in the brain stem and in the cortex, where trypan blue did not appear.

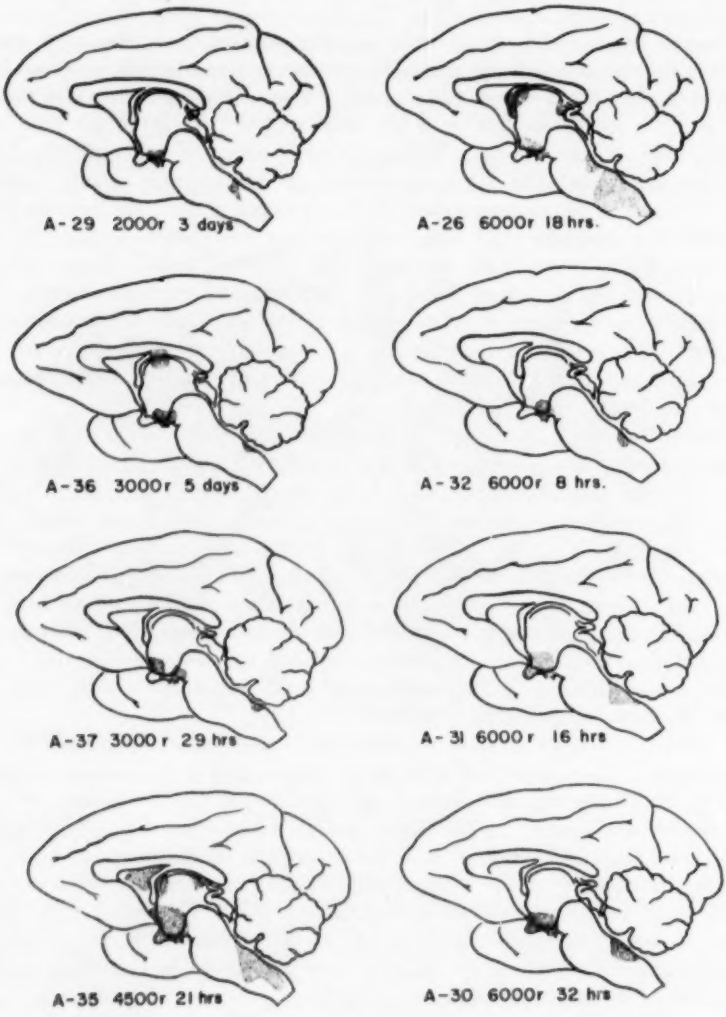

Fig. 2.—Outline drawings of median sagittal views of the brains of eight monkeys. Stippled areas in each case represent the regions of trypan-blue staining, following irradiation of the head. Note the consistency of involvement of hypothalamus and medulla.

In those animals of the 3,000 r series which survived two to three weeks, occasional areas of mononuclear infiltration were seen, occurring frequently as subependymal plaques along the walls of the lateral ventricles and the inferior portions of the third ventricle.

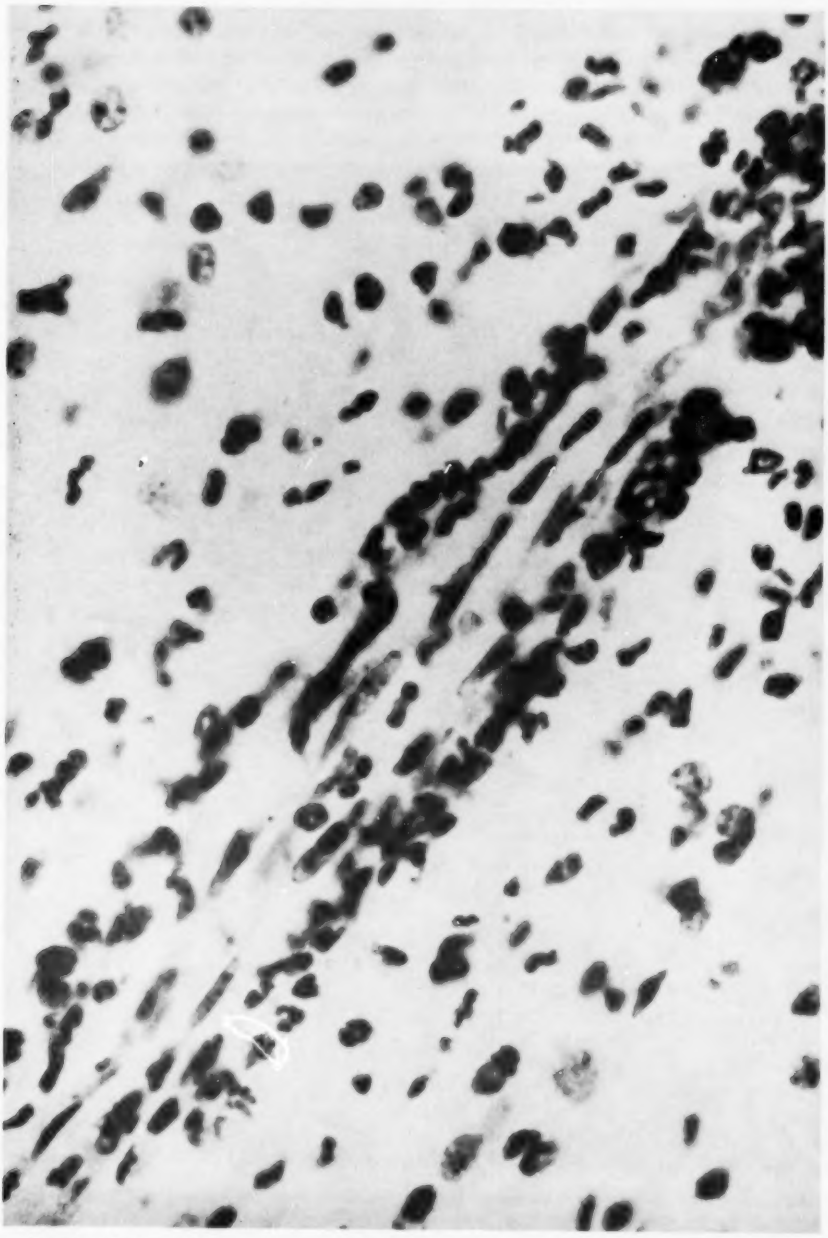

Fig. 3.—Perivascular leucocytic infiltration in the gray matter of the occipital cortex of Animal A-34. This monkey had received 4,500 r to the head and died six hours thereafter. Hematoxylin and eosin stain; × 880.

Animals which died spontaneously after the higher doses of x-radiation showed small perivascular hemorrhages in the cerebral and cerebellar cortices and in the lower brain stem, including the pons and medulla. These apparently were terminal in occurrence, since they were not often seen in animals which were killed. There was no correlation between areas of trypan-blue staining and sites of hemorrhage.

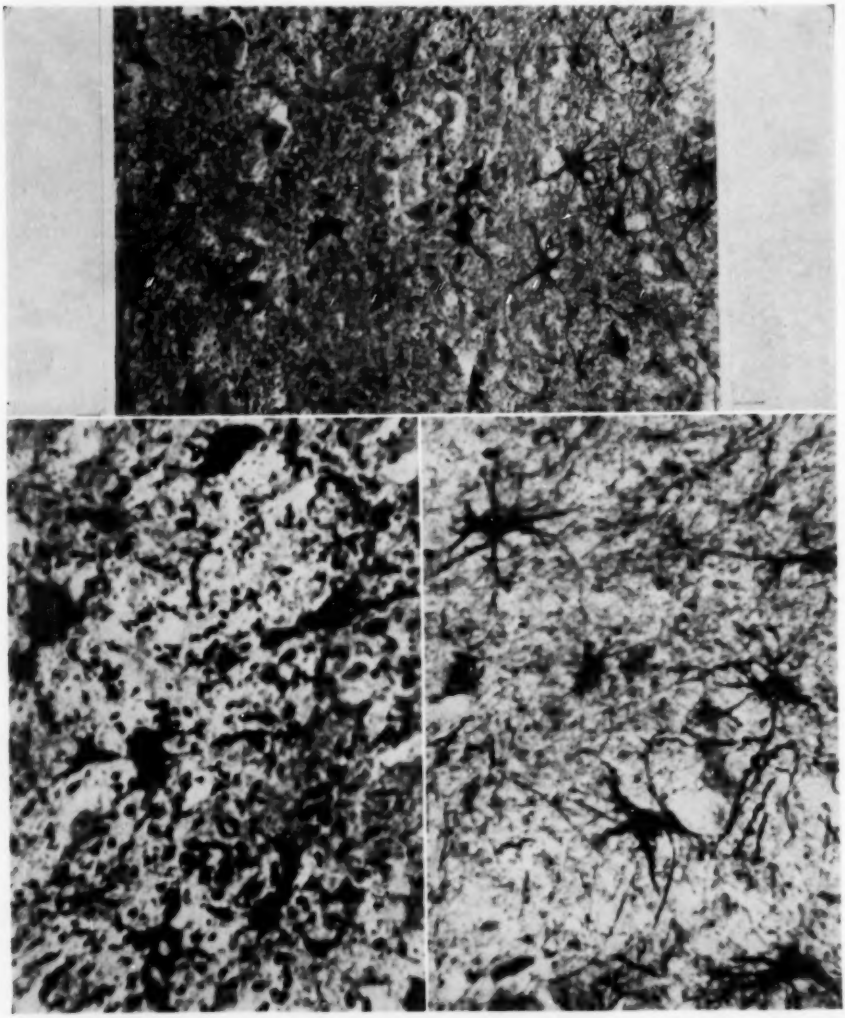

Fig. 4.—Upper: This figure shows an area of transition between normal and disintegrating astrocytes, in the medulla of Monkey A-31, 16 hours after irradiation with 6,000 r. Note the sharp line of demarcation between the disintegrating and the normal cells, which corresponds to the edge of the trypan-blue-stained area. Cajal gold chloride-mercury bichloride stain; × 155.

Lower left: High-power view of degenerating astrocytes seen on the left above. × 490.

Lower right: Higher magnification of normally staining astrocytes on the right above. × 203.

C. Neuroglia. Sections prepared by the gold chloride-mercury bichloride method revealed three rather distinct stages of astrocytic degeneration following irradiation: (1) simple retraction of the cell processes from the walls of the blood vessels without apparent damage either to these processes or to the astrocytic cell body; (2) fragmentation of the processes while the cell body, including the nucleus, still remained definable and (3) disintegration of the entire astrocyte with complete loss of cellular morphology (Fig. 4). The degenerating astrocytes became more hyperchromatic as these stages progressed and were easily distinguished from normally staining cells.

It seems highly significant that areas of trypan-blue staining and of astrocytic degeneration were coextensive and sharply demarcated (Fig. 4). Disintegrating astrocytes were found in the hypothalamus and/or the medulla of every animal receiving 6,000 or 4,500 r. In the hypothalamus such cells were most commonly seen in the supraoptic and paraventricular nuclei and in the dorsal and anterior hypothalamic nuclei and also in the optic chiasm. In two animals degeneration extended into the midline thalamic nuclei, and in one animal the dorsal thalamic nucleus was involved. The internal capsule and basal ganglia were not injured except for the head of the caudate nucleus in one animal. The region most commonly affected in the medulla was at the level of the olive, where astrocytic damage was seen in the medial lemniscus, the entire reticular formation, the nucleus of the spinal tract of the trigeminal nerve, and, dorsally, in the nucleus gracilis, nucleus cuneatus, and the dorsal nucleus of the vagus. The olivary nucleus and the pyramids rarely showed changes in astrocytes.

At doses lower than 4,500 r astrocytic degeneration was less severe than described above for the higher dosage levels, although in four animals receiving 2,000 or 3,000 r very localized damage was observed in the hypothalmic and medullary regions.

Brain sections from one animal in each series were stained by the Penfield combined microglia and oligodendroglia technique. The pathological changes in these cells were not as clear-cut as in the astrocyte. However, two abnormal types of microglia cells were seen in the hypothalamus and medulla of the more heavily irradiated animals. Some cells showed a shortening and thickening of the processes together with a rounding of the cell body, while other microglia cells were disintegrating (Fig. 5). With the stain used only a nonspecific swelling of scattered oligodendroglial cell bodies was seen.

D. Neurons. Various degrees of neuronal injury were observed, including clumping of Nissl substance, chromatolysis, and cell disintegration with neuronophagia (Fig. 6). This degeneration was of equal severity after doses of 6,000 and 4,500 r, was somewhat less intense after 3,000 r, and was very slight in those animals of the 2,000 and 1,500 r groups killed within two weeks after irradiation.

The most severely injured area was the brain stem, followed by the cerebral cortex, with the cerebellum appearing to be least affected. Within the brain stem the hypothalamus and medulla were most intensely damaged, and completely disintegrated neurons were seen only in these areas. The basal ganglia, thalamus, midbrain, and pons contained few to moderate numbers of injured neurons. The diffuseness of the areas showing neuronal damage contrasted sharply with the clear localization of astrocytic degeneration.

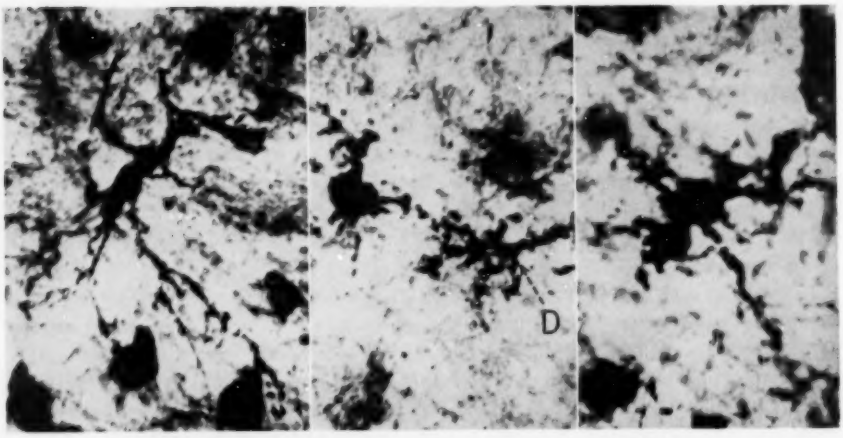

Fig. 5.—Left: Normal microglial cell in the globus pallidus of Animal A-39, killed 36 hours after receiving 6,000 r to the head.

Middle: Two microglial cells in the hypothalamus of the same animal, showing on the left rounding of the cell body and on the right a disintegrating cell, *D*.

Right: Microglial cell in the hypothalamus of the same animal, showing thickening of the processes and rounding of the cell body. Penfield's combined oligodendroglia and microglia method; × 850.

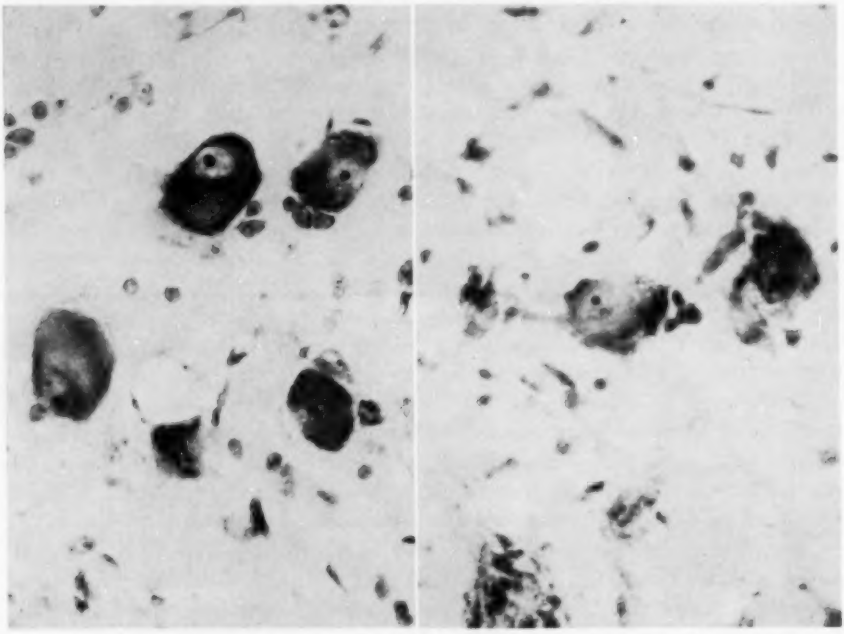

Fig. 6.—Left: Chromatolysis in neurons of the lateral vestibular nucleus, observed 10 days after 4,500 r to the head. Thionine stain; × 222.

Right: Disintegrating neurons in the reticular formation of the medulla in Animal A-31. The area shown corresponds with the area of disintegrating astrocytes in Figure 4. This animal lived 16 hours after receiving 6,000 r to the head. Thionine stain; × 250.

There were brains which did not exhibit an active inflammatory reaction at the time of examination but which did show neuronal pathology. Such injury was considerable in some cases, particularly in those animals which received 3,000 r and died in two to three weeks. There were also areas of the brain, such as the cerebral cortex, which frequently were inflamed but contained few or no chromatolytic neurons.

Regions stained by trypan blue showed the most intense neuronal damage, and such areas were never without degenerating cells. Less intense degrees of neuronal injury, however, occurred in areas not containing trypan blue. To illustrate, the cells

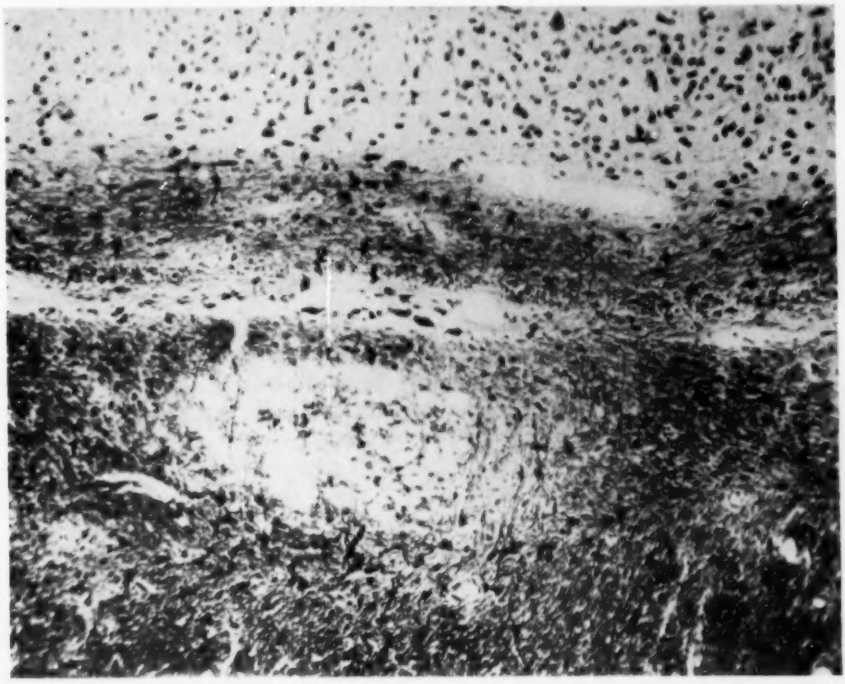

Fig. 7.—Area of degeneration in occipital cortex of Animal A-22, killed five months after exposure of the head to 1,500 r. Note the astrocytic reaction surrounding the lesion site. Cajal gold chloride-mercury bichloride stain. × 76.

of the nuclei of the dorsal portion of the medulla and the reticular formation, where staining with trypan blue occurred, were disintegrating, whereas those in the unstained inferior olivary nucleus showed only chromatolysis.

Observations on Chronic Animals.—In those animals which received 1,500 r and were killed four to eight months after irradiation, the principal change observed was destruction of cortical and subcortical white matter. Pinpoint areas in various stages of degeneration were scattered throughout the frontal, parietal, and occipital cortex, the internal capsule, the pons, and medulla. The more recent of these lesions were characterized by axon swelling, myelin breakdown, and phagocytosis by gitter cells. In animals receiving trypan blue the dye was distributed inter-

cellularly immediately around these more acute degenerative foci. In the older lesions active scar formation was taking place, with areas of gliosis encircling the site of the lesion (Fig. 7). Trypan blue did not stain the tissue around such regions.

Occasionally in the chronic 1,500 r animals there was observed an infiltration of mononuclear round cells similar to that seen in the 3,000 r animals after two or three weeks.

COMMENT

At the dosage levels employed, there appeared to be a direct correlation between the amount of radiation received and the impairment of neurons, neuroglia, and blood-brain barrier. At the lowest dose, 1,500 r, neuronal damage was evident but slight; there was no astrocytic degeneration, and if permeability changes in the blood-brain barrier were present they were too slight to permit staining of the brain by trypan blue. In contrast, at the highest doses, there was extensive injury to neurons, and there were areas of disintegrating astrocytes which corresponded with regions of trypan blue coloration. Neuronal and neuroglial degeneration following ionizing irradiation has been reported by many authors.‖ Vascular permeability changes, however, have not been so consistently demonstrated.

Several hypotheses have been advanced to explain the exclusion of trypan blue from the central nervous system of the normal animal. It has been proposed that the endothelium of the cerebral blood vessels is peculiarly selective and does not permit such substances as trypan blue to enter the nerve tissue.[19] Another view holds that the perivascular feet of astrocytes form a membrane which controls the passage of substances from the blood vessels.# An explanation alternative to the barrier theory suggests that the brain tissue merely lacks affinity for dyes such as trypan blue.[22] In the light of these hypotheses, it is interesting to note that in the irradiated animals of the present study a substance which normally does not penetrate the blood-brain barrier entered the nerve tissue in those areas in which astrocytic degeneration was present.

A variety of chemical and physical agents have been found capable of impairing the blood-brain barrier. Increased vascular permeability resulting in vital dye passage into the brain has been observed after administration of Diodrast,* epinephrine,[26] theophylline,† and hydrogen peroxide.[29] Trauma or simple exposure of the brain has been shown to cause similar permeability changes.‡ Ionizing radiation has been observed to cause trypan-blue staining of perivascular neuroglia in mice [33] and in rabbits.[34] Exposure to x-rays has also been found to increase the permeability of the blood-cerebrospinal fluid barrier.¶ In the present study of monkeys, a sequence of permeability changes was observed in cerebral vessels, (1) edema, (2) perivascular leucocytic infiltration, and (3) penetration of protein-bound vital dyes into the brain stem occurring in that order. The significance of coloration of neural tissue in this last stage lies in the leakage of protein, which occurs only in the presence of severe pathological changes in cerebral vessels. This process may

‖ References 6, 7, 8, 9, 10, 11, 12, and 13.
References 20 and 21.
* References 23, 24, and 25.
† References 27 and 28.
‡ References 30, 31, and 32.
¶ References 35 and 36.

be compared with the sequence of vascular changes observed in the inflammatory reaction of other organs of the body, in which there is, first, a protein-free transudate, then a leucocytic migration, and, finally, a free passage of fluid and proteins from the vessels.

In animals of the present study in which trypan blue entered the brain the predominant foci of staining were the hypothalamus and the dorsal region of the medulla oblongata. It is of interest that these regions are adjacent to areas normally staining with trypan blue, that is, the neurohypophyseal stalk and the area postrema. It is possible that vessels at junctions between structures normally staining with trypan blue and those not so staining have intermediate permeability properties which may be altered readily by ionizing radiation. The proximity of the basally situated trypan-blue-stained regions to large masses of bone and to the lead shield around the neck suggests that these areas may have been subjected to a scattering of soft rays, although this does not clarify the preferential staining of the dorsal part of the medulla. As an alternative explanation, it may be suggested that the positions of the hypothalamus and medulla are such that a general increase in intracranial pressure would press these regions against sharp folds of dura, with resulting local injury.

Areas of trypan-blue penetration and astrocytic degeneration showed severe neuronal damage, although such injury was not limited to stained regions. It is apparent, then, that permeability changes of a degree sufficient to allow trypan blue to escape from the vessels were not prerequisite for the appearance of neuronal damage. That neuronal injury occurred in brains exhibiting edema and inflammatory changes but no trypan blue suggests that the dye method may not be a sufficiently sensitive indicator of permeability changes to permit estimation of the relative importance of direct and indirect neuronal effects. The delayed necrosis of white matter, seen in animals which have been irradiated several months previously, has been observed frequently # and has recently been encountered by Arnold and associates,[38] using finely controlled methods of irradiation.

It was interesting to note that electroencephalograms on animals of this series, taken within the first week after irradiation, showed abnormalities only in monkeys in which there was some evidence of changed cerebrovascular permeability, that is, edema, or leucocytic infiltration, or trypan-blue staining.[14] Also, neuronal degeneration with concomitant EEG changes has been seen in monkeys in which obvious permeability abnormalities were lacking at the time of examination, notably in the 3,000 r animals which lived two to three weeks and in the chronic 1,500 r animals. Some evidence of previous inflammation was present in these monkeys in the form of scattered areas of round-cell infiltration, indicating that earlier changes in permeability may have played some role in the injury of the neurons.

It is felt that the greater radiosensitivity of the hypothalamus and medulla, two extremely vital centers, is a point of particular interest emerging from this work. The striking coincidence of trypan-blue-stained regions with those of astrocytic degeneration is also to be noted, and the severity of neuronal damage in such areas suggests the importance of impairment of the blood-brain barrier following irradiation.

References 7, 11, 13, and 37.

SUMMARY

Single doses of x-radiation ranging from 1,500 to 6,000 r were administered to the heads of 37 monkeys while the remainder of the body was shielded. By means of trypan blue injected intraperitoneally at intervals before and after irradiation, the functional impairment of the blood-brain barrier was studied. Sections of the brains were prepared with various staining methods.

Blood-brain barrier changes, astrocytic degeneration, and neuronal damage were most intense in the 4,500 and 6,000 r monkeys. However, permeability abnormalities and tissue destruction were seen also in the lower-dose groups. The most frequent sites of trypan-blue penetration following irradiation were the hypothalamus and the medulla, in that order. Astrocytic degeneration was confined to areas stained by the trypan blue, while neuronal injury, although severer in these regions, was in general less localized.

In an evaluation of neurological disorders resulting from ionizing radiation to the brain, it is apparent that consideration must be given to the degeneration of astrocytes and the impairment of the blood-brain barrier as factors involved in producing neuronal injury.

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EFFECT OF ATROPINE ON BLOOD PRESSURE OF PATIENTS WITH MENTAL AND EMOTIONAL DISEASE

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CONCOMITANT with the psychological signs and symptoms of schizophrenia are many physiological disturbances. These, among others, include vasomotor changes, excessive salivation, cardiovascular dysfunction, and pupillary abnormalities, which clearly implicate the autonomic nervous system. Much excellent research * has more directly involved both the sympathetic and the parasympathetic components of the autonomic system: Claims are registered that the reactivity of the autonomic system is normal [5] as measured by known methods or that it is sluggish.† The decreased reactivity of the schizophrenic to cold is ascribed to the diminished secretion of epinephrine and the deficient or disordered output of adrenocortical factors, which similarly accounts for the diminished elevation of the blood sugar in response to stress.[3]

There is a tendency to emphasize either the sympathetic nervous system [6] or the parasympathetic nervous system.‡ In the acute phases sympathetic predominance does appear to be present.§ Nevertheless, injections of blood from excited schizophrenics into hypophysectomized-adrenomedullated rats induced hypoglycemia, strong evidence for increased parasympathetic activity.[2] There probably is relative inequality of these two systems, but the two components are not in reality antagonists; they are synergists.‖ The parasympathetic system through its chemical mediator acetylcholine controls the activity of sympathetic ganglia and thus the output of epinephrine (and arterenol [nor-epinephrine]). Epinephrine, in turn, affects parasympathetic function.[8] Thus, by a push-pull relationship both systems are maintained in balance. If there is parasympathetic overactivity, one would expect to find evidence for sympathetic overactivity if measured against the base line of that person's sympathetic activity when well. Yet parasympathetic activity would be relatively greater as compared with sympathetic activity, and one would erroneously conclude that sympathetic activity was low.

Testing the reactivity of schizophrenic patients to autonomic drugs has yielded some measure of success in differentiating subtypes of schizophrenia by epinephrine, pilocarpine, and atropine [10] and in predicting response to electroconvulsive therapy.[7]

With the cooperation of the Saskatchewan Committee on Schizophrenia Research.
The study was supported by the Department of National Health and Welfare, Canada.
Director of Psychiatric Research, Psychiatric Services Branch, Department of Public Health.

* References 1, 2, 3, and 11.
† References 2 and 3.
‡ References 1 and 2.
§ References 6 and 7.
‖ References 8 and 9.

Recent investigations [11] have shown that the blood pressure response will indicate with a high degree of accuracy the response of depressed and schizophrenic patients to E. C. T. irrespective of diagnosis.[11] The sample tested falls into seven groups. Schizophrenics are fairly equally distributed among all groups, and depressions cluster in Groups 6 and 7. Schizophrenics in the latter groups respond favorably to E. C. T. These findings are most valuable, but they do not necessarily measure the reactivity of the autonomic nervous system, as has been claimed. Obviously, the reaction of the body to injected epinephrine measures the reactivity of the end-organs and of the countermechanisms to epinephrine action, not reactivity of the sympathetic system, of which epinephrine is the product.[5]

A test of central autonomic reactivity must afford evidence of ability to respond to stimuli by the production of chemical mediators. The parasympathetic nervous system might be tested by subjecting the individual to stimuli that are stressful and then measuring parasympathetic response when sympathetic activity is blocked. The sympathetic system might be tested by increasing acetylcholine concentration, which controls the sympathetic ganglia, and thus the concentration of arterenol and epinephrine.

Acetylcholine exerts control over epinephrine production by its nicotinic activity. Metacholine (Mecholyl) has weak nicotinic activity [12] and exerts little direct push on the adrenal medulla and other sympathetic ganglia. Acetylcholine is so rapidly inactivated that it cannot be effectively used. However, atropine appears to fulfill the criteria for an autonomic drug which will test the reactivity of the sympathetic centers. Atropine blocks the muscarinic activity of acetylcholine but leaves unimpaired the nicotinic activity. By increasing the concentration of acetylcholine, it should gently push the adrenal medulla and other ganglia. The sympathetic response would be measured by the change in systolic blood pressure. An increase in blood pressure would indicate reactivity, whereas no elevation of blood pressure would indicate no sympathetic response to atropine.

The hypothesis was developed that the response to atropine would differentiate mental disorders. If schizophrenia is marked by sympathetic underreactivity, the schizophrenics would show no increased secretion of epinephrine, and thus no elevation of systolic pressure, whereas other categories with normally reactive sympathetic ganglia would respond by an elevation of systolic pressure.

MATERIAL AND METHODS

Patients tested included those admitted to the Munroe Wing of the Regina General Hospital and patients from Saskatchewan Hospital, Weyburn, both acute and chronic. Normal controls included medical students of the University of Saskatchewan and members of the staff of the Munroe Wing.

The Munroe Wing is a psychiatric ward of the Regina General Hospital, which is a 39-bed treatment center with a mean hospitalization period of about four weeks. Patients of all diagnostic categories are admitted provided they are sufficiently cooperative to be housed in an open ward. Psychotherapy is short-term, dynamically oriented. The patient population consists of approximately one-third schizophrenics and two-thirds with other diagnoses. Nearly all the neurotic population reported here are Munroe Wing patients.

The Saskatchewan Hospital, Weyburn, is a representative mental hospital housing about 1,900 patients, most of them psychotic. It has admission wards for acute illnesses and wards for chronic patients. Certification by two physicians is the commonest method of admission.

Acute schizophrenics are treated at both Munroe Wing and Saskatchewan Hospital, Weyburn. However, although both groups draw from essentially the same population, there is a

marked difference in the samples obtained by the two units. At the psychiatric ward the schizophrenics are oftener early cases and are frequently labeled neurotic by referring physicians who are not psychiatrists, and they are oftener cooperative. Also, they include more first

TABLE 1.—*Mean Systolic Blood Pressure Response of Several Psychiatric Diagnostic Groups to Atropine*

Diagnosis	No. of Patients	Blood Pressure, Mm. Hg							
		Minutes After Injection							
		—5	0	5	10	15	20	25	30
Schizophrenics									
Munroe acute	64	132	130	128	128	127	127	127	126
Weyburn acute	47	127	127	126	126	125	125	123	124
Weyburn chronic	67	129	129	129	128	127	127	128	128
Normals	30	119	119	120	123	127	128	129	128
Neuroses	33	115	117	120	123	124	124	122	123
Depressions	32	119	119	120	123	124	125	126	125
Psychopaths	35	118	118	117	119	122	123	123	123
Epilepsy	12	115	115	115	117	116	116	118	117
All schizophrenics	178	130	129	128	127	126	126	126	126
All others	142	117	118	119	122	123	124	124	124

TABLE 2.—*Mean Diastolic Blood Pressure Response of Several Psychiatric Diagnostic Groups to Atropine*

Diagnosis	No. of Patients	Blood Pressure, Mm. Hg Blood Pressure, Mm.							
		Minutes After Injection							
		—5	0	5	10	15	20	25	30
Schizophrenics									
Munroe acute	64	82	81	81	82	85	85	87	88
Weyburn acute	47	80	80	79	80	81	82	83	83
Weyburn chronic	66	88	88	90	88	89	90	92	92
Normals	30	75	75	76	78	82	87	89	89
Neuroses	32	78	77	79	83	82	84	81	87
Depressions	32	78	78	79	82	87	88	88	88
Psychopaths	35	73	73	73	75	80	83	84	85
Epilepsy	12	71	70	71	74	75	79	79	80

TABLE 3.—*Mean Pulse Rate Response of Several Psychiatric Diagnostic Groups to Atropine*

Diagnosis	No. of Patients	Pulse Rate							
		Minutes After Injection							
		—5	0	5	10	15	20	25	30
Schizophrenics									
Munroe acute	64	88	87	82	97	109	116	115	120
Weyburn acute	47	80	79	79	84	91	97	99	101
Weyburn chronic	67	78	77	77	79	84	93	96	98
Normals	30	72	72	71	81	93	106	108	108
Neuroses	32	79	79	77	98	110	114	115	114
Depressions	33	74	73	69	81	95	100	106	104
Psychopaths	35	75	75	72	80	92	100	105	105
Epilepsy	11	75	75	71	82	97	104	108	111

admissions. Most of the admissions to the other hospital are more obviously mentally ill and are so recognized by the certifying physician. They include a higher proportion of excited schizophrenics and schizophrenics who have not responded to short-term therapy. More readmissions are represented. The chronic patients have been hospitalized between 2 and 30 years and have not responded to any recognized psychiatric therapy.

TABLE 4.—*Change in Blood Pressure and Pulse Rate Produced in Several Psychiatric Diagnostic Groups, in 30 Minutes, by Atropine*

Diagnosis	Change in Pressure, Mm.		Change in Pulse Rate		
	Systolic	Diastolic	5 Min.	30 Min.	Increased
Schizophrenics					
Munroe acute	−6	+ 6	−6	+32	38
Weyburn acute	−3	+ 3	−1	+21	22
Weyburn chronic	−1	+ 4	−1	+20	21
Normals	+9	+14	−1	+36	37
Neuroses	+8	+ 9	−2	+35	37
Depressions	+6	+10	−5	+30	35
Psychopaths	+5	+12	−3	+30	33
Epilepsy	+2	+ 9	−4	+36	40

TABLE 5.—*Effect of Change in Clinical State of Schizophrenia on Atropine Response*

	No.	Time							
		−5	0	5	10	15	20	25	30
		Minutes After Atropine							
Munroe									
Improved	15	127	125	126	128	129	129	130	130
Not improved	5	129	131	131	130	127	128	127	127
Weyburn									
Improved	8	129	130	129	128	132	133	133	134

TABLE 6.—*Means, Standard Deviations of Means, and Correlation Coefficients Between Systolic and Diastolic Pressure Before and After Atropine*

		No.	Systolic		Diastolic		r
			Mean	S. D.	Mean	S. D.	
Munroe schiz.	B	118	130.0	15.9	80.9	11.7	0.80
Acute	A	112	125.1	16.2	86.9	12.6	0.81
Munroe schiz. after treatment	B	22	128.0	17.6	80.5	11.6	0.50*
Improved	A	22	130.0	15.0	90.5	10.3	0.62
Weyburn schiz.	B	84	128.0	15.2	80.7	11.2	0.37
Acute	A	84	123.9	12.9	83.7	12.0	0.51
Weyburn schiz.	B	132	128.9	17.4	88.3	16.8	0.61*
Chronic	A	134	125.8	24.3	90.6	19.6	0.79
Neuroses	B	56	118.1	12.8	78.3	8.4	0.59
	A	51	123.6	11.8	87.5	8.5	0.74
Psychopaths	B	62	118.9	16.4	73.1	11.5	0.63*
	A	62	124.0	16.7	85.0	13.9	0.78
Depressions	B	54	119.0	14.1	78.2	9.6	0.73
	A	50	127.6	15.1	88.8	10.6	0.77
Normals	B	60	119.2	9.8	74.5	8.7	0.37*
	A	60	127.3	8.2	89.0	9.4	0.61

* Difference between r values has probability of 0.1 of not being significant.

At the Munroe Wing the patient's response to atropine was determined a few days after admission to the hospital. Most of them were still undiagnosed. Clinical diagnosis was established by the clinical staff, who were not informed of the results of the atropine test. After discharge the final diagnosis was used as a basis for comparison. At Weyburn the physician in charge of a female admission ward tested all male admissions and vice versa.

The following testing procedure was established: The subject was brought into the testing room at 9 a. m. After he had rested 5 to 10 minutes the sphygmomanometer was applied. During this interval the patient was reassured and advised that he would be given an injection of atropine and what he might expect from it, such as dryness of mouth and throat and blurring of vision. Then readings of systolic and diastolic pressure and pulse rate were recorded every five minutes. Systolic pressure was carefully determined by slowly allowing the pressure to fall until the first audible sustained sound was heard. Recordings were made to the nearest 5 mm. of mercury. At the end of five sets of readings (20 minutes) 3 mg. of atropine sulfate was injected intramuscularly. Readings were then continued every 5 minutes for 35 minutes. The results were plotted immediately on squared paper containing 100 squares per square inch.

TABLE 7.—*Distribution of Atropine Responses, Whether Up or Down, Within Psychiatric Groups*

Diagnosis	Total No.	No. with Pressure Down	Percentage
Munroe schizophrenics			
Acute	64	56	88
Weyburn schizophrenics			
Acute	47	34	72
Weyburn schizophrenics			
Chronic	67	42	63
Epilepsy	12	8	67
Psychopaths	35	11	31
Neuroses	33	5	15
Depressions	32	7	22
Normals	30	6	20

RESULTS

The mean systolic pressures for all the groups tested are given in Table 1. The pressure of the schizophrenic groups decreased, in contrast to that of all other groups. Mean diastolic pressures and pulse rates are given in Tables 2 and 3. There was no differential response in these two variables. Table 4 shows the change in these variables induced by the atropine.

A few schizophrenics at the Munroe Wing and at Weyburn were again tested after treatment. The results are shown in Table 5.

The readings taken at —5 and 0 time were compared with readings taken at 25 and 30 minutes. Means, standard deviations, and correlation coefficients for systolic and diastolic pressures are shown in Table 6.

The distribution of responses within each group between those whose systolic pressure rose and those whose systolic pressure remained unchanged or fell is shown in Table 7.

COMMENT

The systolic pressure of the schizophrenic group decreased in response to atropine. This was most pronounced with acute schizophrenics of the Munroe Wing. The systolic pressure of the chronic schizophrenics decreased slightly. In contrast, all other groups showed an increase in pressure. The diastolic pressure increased in all groups, as did the pulse rate.

The schizophrenic groups differed from other groups, as shown by the decrease in systolic pressure, by the decreased elevation of diastolic pressure, and by a slighter increase in pulse rate. The Munroe Wing acute schizophrenics were in general more reactive than the Weyburn acute schizophrenics; e. g., pulse elevation from the 5-minute depression to the 30-minute elevation was 38, as compared with 22. The two Weyburn groups showed least elevation of pulse rate as compared with all other groups. The Weyburn acute schizophrenics most closely resembled the Weyburn chronic schizophrenics. Perhaps this is a result of the increased chronicity of Weyburn acute schizophrenics, as compared with Munroe acute schizophrenics. It is evident that there is a continuous response with Munroe Wing acute schizophrenics, at one end, and the Weyburn chronic group, at the other, with the Weyburn acute group in between.

All other groups showed greater increases in diastolic pressure and pulse rate.

Injection of 3 mg. of atropine sulfate caused an increase in systolic blood pressure in 80% of normals tested. Neurotic and depressed subjects gave a similar response. In acute schizophrenics the percentage of subjects with increase in systolic pressure varied from 12, for the Munroe schizophrenic group, to 28, for the Weyburn group. There, thus, is a clear difference in the response of these two groups. The atropine response therefore has diagnostic implications. Chronic schizophrenics usually present fewer diagnostic difficulties than acute schizophrenics. Similarly, EEG studies are diagnostic for the majority of people with epilepsy. If these two groups, and also psychopaths (a group not yet characterized physiologically), are excluded from our series, it appears that any person showing a decrease in systolic pressure after atropine will be schizophrenic four out of five times. Any subject whose pressure response is upward has only one chance out of four of being schizophrenic. These observations apply to populations that do not markedly differ from ours.

Epileptics, on the basis of the small sample, tend to fall in with the schizophrenic population. The psychopath group appears to be a group of its own. It is possible that it is a heterogeneous group, which may include within it undiagnosed schizophrenia of recent onset or unrecognized anomalous early schizophrenia.

As normals respond to atropine with increased systolic pressure and schizophrenics with decreased pressure, we might expect a reversal to occur in a group of schizophrenics who have become well. This is confirmed by results in Table 5.

Hoskins postulated a rigid vascular system for schizophrenics to explain a remarkably high correlation between systolic and diastolic pressure. With this study, the highest correlations were observed with the Munroe acute schizophrenics, confirming Hoskins' reports. Weyburn acute schizophrenics appear to be, once more, a different sample of the population, with much lower correlation coefficients.

After treatment Munroe acute r values decreased toward normal. Other categories showed values higher than normal. The hypothesis that the schizophrenic vascular systems react like rigid tubes perhaps may be extended to other groups of illnesses. Perhaps any illness which produces stress in the subject decreases freedom of reactivity of the vascular system. The addition of atropine produces an increase in the correlation coefficient at the 0.1 probability level for all groups but the acute schizophrenics and the depressions. Thus, an autonomic drug which

is known to interfere with autonomic function tends to produce a more rigidly acting vascular system. Where the system is already rigid atropine does not increase rigidity much.

The hypothesis that in schizophrenia the sympathetic nervous system is less responsive than in other categories is reinforced.

SUMMARY

When 3 mg. of atropine sulfate was administered to each of 320 subjects, it was found that the response of the diastolic pressure and pulse rate did not differentiate various diagnostic groups, whereas the systolic pressure response did. In acute schizophrenics, chronic schizophrenics, psychopaths, epileptics, and other groups, including normals, the proportion showing decrease in pressure were 81, 63, 31, 76, and 19% respectively. In schizophrenic groups atropine produced a decrease in temperature. In other groups it did not.

The correlation between the systolic and the diastolic pressure was higher in all categories than in normals. Atropine increases the correlation.

Dr. J. Smythies and Dr. J. Lucy performed the atropine tests; Dr. D. Hutcheon tested the normals at the University of Saskatchewan School of Medicine, Saskatoon; Dr. H. Osmond, Superintendent, Saskatchewan Hospital, Weyburn, by his collaboration, ensured the completion of this research, and Dr. B. Gaerber, Clinical Director, Munroe Wing, cooperated in the research.

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ROLE OF INTRATHECAL DETERGENTS IN PATHOGENESIS OF ADHESIVE ARACHNOIDITIS

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ADHESIVE arachnoiditis following spinal anesthesia is a well-recognized entity and has been well documented by Kennedy and associates,* Yaskin and Alpers,[3] and Thorsen.[4] The reason for its development is not clear, and it has been variously attributed to the effects of the anesthetic, to impurities, and to associated infection. It is possible that the cause is not the same in all instances, but experience with a fatal case of extensive, severe adhesive arachnoiditis raised the possibility that a hitherto not widely recognized pathogenic agent may have played an inciting role. The agent in question was a commercially available detergent cleaning material, Alconox, which had been used in the preparation of the anesthetic equipment. It is possible that the Alconox alone or the synergistic action of a surface-active agent and the anesthetic may have been responsible for the arachnoiditis.

REPORT OF A CASE

History.—S. F., a 54-year-old married white man, entered another hospital on Nov. 4, 1948, complaining of substernal pain, substernal oppression, and dyspnea, which came on after a tooth extraction. The pain was relieved only by hypodermic analgesic medication. Examination at that time was normal, and the preliminary impression was that of an acute myocardial infarction. The hemogram, urine, and sedimentation rate were normal. Serial electrocardiograms were normal. A cholecystogram revealed calculous cholecystitis. The patient was discharged Nov. 10, with a final diagnosis of calculous cholecystitis. He was readmitted to the hospital 15 months later, on March 2, 1950, complaining of severe right upper quadrant abdominal pain with radiation of pain posteriorly around the costal cage into the mid-dorsal area, continuing severe and unremitting for 36 hours. The past history revealed some hesitancy on initiation of urination for about one year. Physical examination revealed bilateral costovertebral angle tenderness and right upper quadrant abdominal tenderness. On March 7, five days after admission, cholecystectomy and appendectomy were performed, using thiopental (Pentothal) sodium and spinal anesthesia. The spinal anesthetic agent was tetracaine hydrochloride diluted with 3.5 cc. of 10% glucose and introduced into the subarachnoid space at the fourth lumbar interspace, without difficulty. After operation the patient appeared depressed, and an atonic, distended bladder was observed. This complication required repeated catheterization. Because of the continuing faulty detrusor activity, he received bethanechol (Urecholine) therapy. He was discharged from the hospital 14 days after operation, on March 21, with a final diagnosis of calculous cholelithiasis treated by cholecystectomy. There was also considered the possibility of a post-spinal-anesthesia cauda equina syndrome.

He was readmitted to the hospital three days later, on March 24, complaining of bilateral calf pain and chest pain. Examination revealed bilateral calf tenderness and a bilateral Homans

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* References 1 and 2.

sign. The initial impression was that of bilateral phlebothrombosis, for which he received bishydroxycoumarin (Dicumarol) therapy. At that time it was noted that the patient still had an atonic, distended bladder, but that there was a partial response to bethanechol injected subcutaneously. He was discharged after 11 days, on April 4, with a final diagnosis of bilateral postoperative thrombophlebitis. After discharge from the hospital he continued withdrawn, apathetic, incontinent, and completely disinterested in his environment. He had marked difficulty in the formulation of his speech, complaining of inability to remember what he wanted to say. His urinary incontinence persisted. At no time did he become aggressive or demonstrate abnormal thought processes. One week prior to admission to the Jefferson Medical College Hospital, he was seen by a psychiatrist, received a diagnosis of "involutional depression," and was treated by means of an electric shock. Twelve hours after this therapy he experienced a spontaneous generalized clonic-tonic convulsive seizure with urinary incontinence. He was temporarily hospitalized at another institution and was transferred to the Jefferson Hospital on April 24.

Examination.—The patient was a well-developed, fairly well-nourished man who was apathetic and devoid of spontaneity. He never moved or spoke unless urged to do so. His speech was hesitant and dysarthric; his replies were not always pertinent, and he was disoriented for time, place, and person. He was incontinent of feces and urine. The optic fundi were normal. The visual fields could not be evaluated. The pupils were small and reacted sluggishly to light, and over a narrow arc. There was no weakness of the face, palate, or tongue, but there was a coarse tremor of the tongue on protrusion. He had no apparent motor weakness, but evaluation was difficult, due to mental torpidity. Cerebellar tests could not be evaluated, for the same reason. Sensation could not be fully evaluated, but the patient responded everywhere to painful stimuli. There was a coarse tremor of the outstretched hands. The deep reflexes were overactive and equal, and no pathological reflexes were elicited.

Examination of the abdomen revealed a well-healed incisional scar in the right upper quadrant. Rectal examination revealed loss of sphincter tone and slight enlargement of the prostate gland. The initial clinical impression was that of dementia paralytica, with frontal-callosal tumor and Alzheimer's disease to be excluded.

Laboratory Studies.—The hemogram was normal. Urinalysis revealed an occasional pus cell and 1 to 5 red blood cells in the urinary sediment per high-powered microscopic field. The blood urea nitrogen and fasting blood sugar were normal. The blood Wasserman and Kahn reactions were negative. Roentgenograms of the skull and chest were negative. Cerebrospinal fluid obtained from the cisterna magna revealed 14 cells per cubic millimeter, with a negative Wassermann reaction and colloidal gold curve.

Clinical Course.—The patient continued to be apathetic, incontinent of feces and urine, and completely devoid of spontaneity. He had to be fed, and it was noted that he had to be told to swallow, for otherwise he either held the food in his mouth or chewed the food constantly. Lumbar puncture was attempted on several occasions, but no cerebrospinal fluid was obtained. A cisternal puncture revealed clear fluid whose analysis was previously listed. The patient became slightly more alert after this procedure but still exhibited a profound organic mental syndrome. Pneumoencephalography was attempted, but no exchange of cerebrospinal fluid could be achieved. A ventriculogram was performed and revealed symmetrical, massive dilatation of all four ventricles (Fig. 1). The patient suddenly ceased to breathe at 9:15 a. m. on the morning following ventriculography, and 63 days after his spinal anesthesia.

Necropsy.—General postmortem examination revealed a terminal pneumonia with acute pulmonary congestion and edema, mild coronary atherosclerosis with focal myocardial fibrosis, moderate to severe aortic atherosclerosis, passive congestion of the spleen, mild arteriosclerosis of the kidney with acute congestion and a retention cyst, colloid adenoma of the thyroid, and acute suppurative prostatitis.

The brain weighed 1,320 gm. and measured 19 by 15 by 8 cm. There was thickening of the leptomeninges of the base, which was particularly pronounced around the optic chiasm and the anterior portion of the circle of Willis. At the base of the medulla and pons and over the quadrigeminal plate, the arachnoid appeared greatly thickened and adhesive and merged imperceptibly with the emergent cranial nerves (Fig. 2). Coronal sections of the formalin-fixed brain showed edema of the brain. Dilatation of all the ventricles was noticeable. There were

punched-out holes in the gray and white matter of both hemispheres, and cheesy, soft material was present in the ventricular system. This material had the odor and appearance of a postmortem autolytic change. No gross lesions of the cerebellum or brain stem were detected on transverse sectioning.

The spinal cord measured 32 cm. in length. The dura was intact. The undersurface of the dura was extremely adherent to the underlying structures and stripped with great difficulty. The arachnoid over the entire dorsolateral surface of the cord appeared cloudy, thickened, and tightly adherent to the dura and cord substance. The cauda equina and conus medullaris were grossly normal.

Microscopic Study: Sections of celloidin-imbedded material prepared with the hematoxylin and eosin stain, the Weigert stain, and the toluidine blue stain were examined. The cerebral cortex showed moderate thickening of the leptomeninges with moderate mononuclear cell infiltration. The meningeal blood vessels appeared normal. The ganglion cells stained poorly, showed attenuation of their apical dendrites, had marked Nissl substance alteration, and were absent in a patchy fashion. Numerous areas of postmortem autolysis were encountered. There were scattered changes in the cortical arterioles, with thickening and hyalinization of the

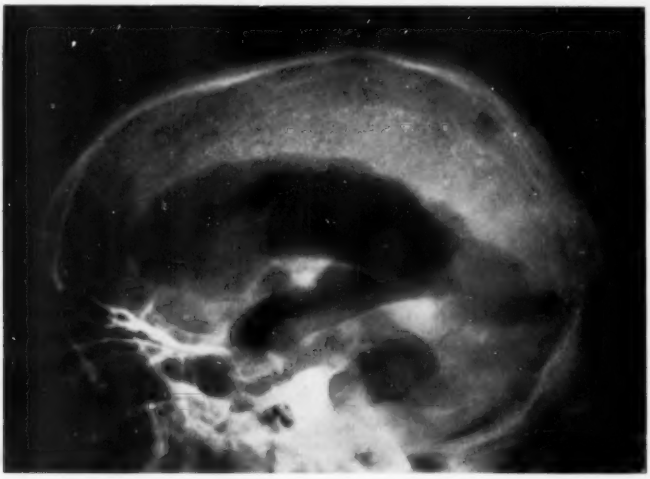

Fig. 1.—Ventriculogram, showing massive dilatation of entire ventricular system.

arteriolar walls. Silver stains failed to indicate the presence of senile plaques. Sections at the region of the striate body were normal, save for involvement of the optic tract in a matted adhesive mass as it passed the temporal region. This mass was composed of fibroblastic proliferation and was infiltrated with mononuclear cells. The left lateral ventricle was markedly dilated.

Sections through the thalamus and mesencephalon revealed slight meningeal thickening and sparse mononuclear cell infiltration of the meninges. Sections through the medulla at the level of the inferior olive revealed massive arachnoidal proliferation with blockage of the lateral recesses of the fourth ventricle (Fig. 3). Sections through the medulla at the level of the pyramidal decussation showed fibroblastic arachnoidal proliferation involving the basilar vessels and mononuclear cells infiltrating the membrane. The fasciculus gracilis showed definite demyelination at this level (Fig. 4*A* and *B*).

Sections through the cervical, thoracic, lumbar, and lumbosacral regions of the spinal cord revealed an extensive, proliferative adhesive arachnoiditis enmeshing the nerve roots and in spots binding the dura mater to the spinal cord (Figs. 5 and 6). This reaction was much more pronounced in the posterior portions of the spinal cord than in the anterior portions. Examination of the Weigert stains revealed spotty demyelination of the anterior and posterior roots

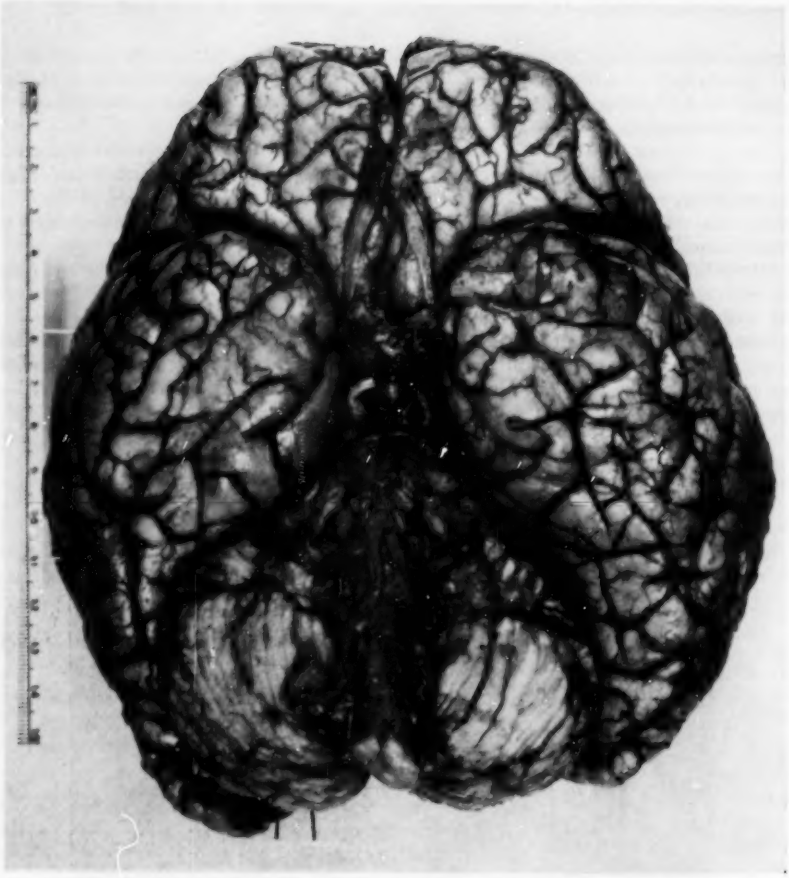

Fig. 2.—Basal view of brain, showing marked thickening of basilar leptomeninges.

Fig. 3.—Section of medulla at level of inferior olive, showing proliferation of leptomeninges in lateral recess. Toluidine blue; × 6.

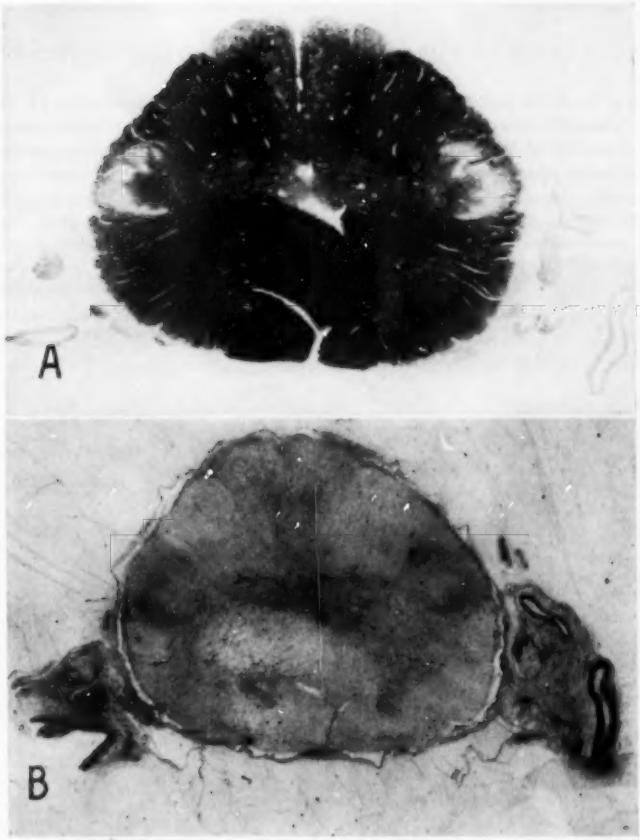

Fig. 4.—*A*, section of medulla at level of pyramidal decussation, showing demyelination of fasciculus gracilis. Weigert stain; × 6. *B*, section at level of pyramidal decussation, showing thickening of leptomeninges. Toluidine blue stain; × 6.

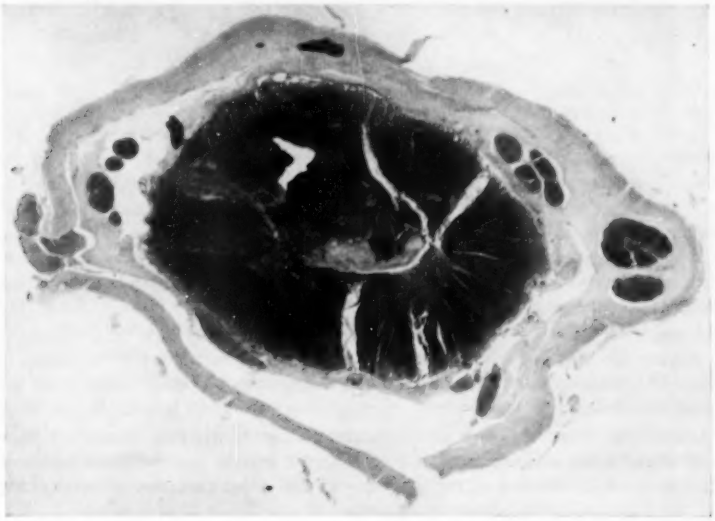

Fig. 5.—Cervical spinal cord, showing marked thickening of meninges and peripheral demyelination of cord. Large areas of cleavage in the cord parenchyma are fixation artifacts. Weigert stain; × 6.

and demyelination of the periphery of the spinal cord—status spongiosus (Fig. 7). Hematoxylin-eosin stains showed a fibroblastic proliferation, with a thick carpet of collagenous fibers and an increased number of fibroblastic nuclei. There was a scanty infiltration of the dura by small mononuclear cells, which had a sparse cytoplasm. Occasionally there were large cells with a more abundant cytoplasm and large, deeply stained nuclei. The subarachnoid space appeared partially obliterated, particularly in the posterior portion of the spinal canal, by a marked fibroblastic proliferation. In some portions of the spinal cord the fibroblastic proliferation was adherent to the inner surface of the dura mater. Some areas showed an areolar, loose connective tissue response, while most areas of proliferation showed closely interlocked, matted collagenous fibers, which closely adhered to the outer surface of the spinal cord and merged imperceptibly with the parenchymatous pia mater of the spinal cord (Fig. 7*B*). Occasionally there were seen calcified blood vessels in this mass, and the degenerative changes involved all

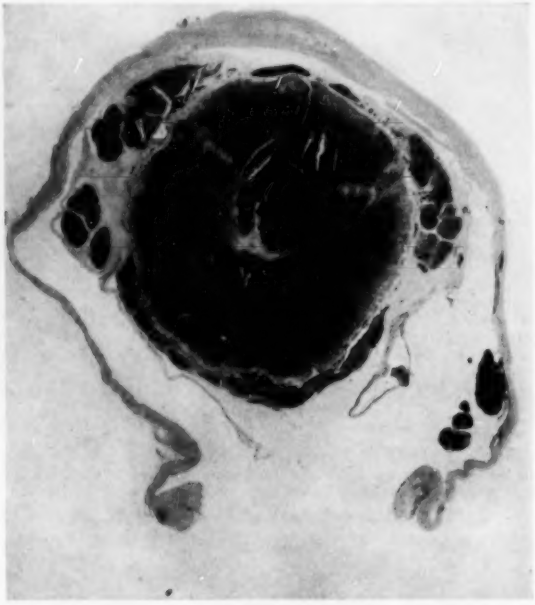

Fig. 6.—Lumbar spinal cord, showing thickened meninges, demyelination of dorsal nerve roots, and demyelination of cord periphery (status spongiosus). Weigert stain; × 6.

the vascular layers. The calcium in blood vessels appeared to be predominantly in the tunica adventitia. The dorsal and ventral nerve roots were enmeshed in the fibrous connective tissue stroma. There were a few areas of fresh hemorrhage in the leptomeninges, but these showed well-outlined red blood cells and no evidence of degenerating blood pigment. The blood vessels of the spinal cord generally showed no degenerative changes. There was infiltration of the tissue stroma by large and small lymphocytes. These cells were particularly apparent in the pia-arachnoid near the spinal cord.

Nissl stains of the spinal cord revealed alteration of anterior horn cells without apparent loss in number of cells, but with the anterior horn cells pyknotic and showing loss of Nissl substance. The neurons showed extrusion and eccentricity of their nuclei, and occasional shadow cells were seen.

The anatomical diagnoses were adhesive arachnoiditis of the base of the cerebrum, brain stem, and spinal cord; demyelination of the fasciculus gracilis and fasciculus cuneatus at the medullary level; demyelination of the periphery of the spinal cord throughout its length, due

to the adhesive arachnoiditis; demyelination of the dorsal and ventral nerve roots of the spinal cord, subsequent to the arachnoiditis; internal hydrocephalus, due to occlusion of the medullary foramina subsequent to the adhesive arachnoiditis, and cerebral arteriosclerosis.

Summary.—A 54-year-old-white man had tetracaine spinal anesthesia for the performance of a cholecystectomy. In the immediate (24-48 hour) postoperative period bladder dysfunction,

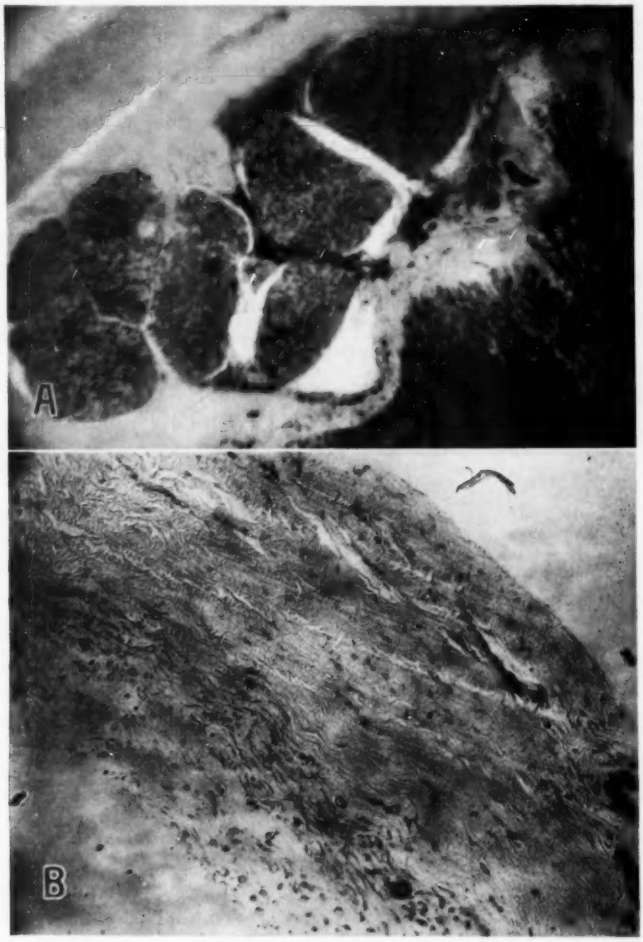

Fig. 7.—*A*, dorsal nerve roots of lumbar cord, showing marked demyelination. Weigert stain; × 50. *B*, view of meninges to show fibroblastic proliferation and scanty round-cell infiltration. Toluidine blue stain; × 200.

radicular pain, and an organic mental syndrome developed. Neurological examination revealed apathy, an organic mental syndrome, sphincteric incontinence, small sluggish pupils, and overactive but equal deep reflexes. Laboratory studies were normal save for pus and red blood cells in the urinary sediment. Cerebrospinal fluid obtained via the cisternal route showed 14 cells per cubic millimeter, a negative Wassermann reaction, and a negative colloidal gold curve.

Ventriculography was performed and revealed symmetrical, massive dilatation of the entire ventricular system. The patient died 24 hours after this procedure, and 63 days after the spinal anesthesia.

Autopsy revealed terminal pneumonia, coronary and aortic atherosclerosis, and severe adhesive arachnoiditis involving the base of the brain, the brain stem, and the spinal cord. Neuropathological examination revealed dilatation of the ventricular system and occlusion of the lateral recesses of the fourth ventricle by fibroblastic proliferation. The dura mater was adherent to the cord, and there was a profound proliferative adhesive arachnoiditis, with scanty round-cell infiltration involving the brain stem and spinal cord. The anterior and posterior nerve roots, fasciculus gracilis, and periphery of the spinal cord showed demyelination. The anterior horn cells showed chromatolysis and nuclear changes.

We have presented the case of a man in whom there developed what appeared to be clinically a cerebral syndrome with emotional and intellectual deterioration, and who had an extensive adhesive arachnoiditis producing a marked internal hydrocephalus and spinal cord changes. His symptoms came on acutely after he had received spinal anesthesia and continued relentlessly until his death, 63 days after spinal anesthesia.

COMMENT

The case described shows an extensive, severe adhesive arachnoiditis which ended fatally and was verified by postmortem examination. Though there are numerous reports of arachnoiditis following spinal anesthesia, few of these give pathological findings.

Verified Cases of Adhesive Arachnoiditis (Table).—Lindemulder [5] reports two cases of patients expiring after spinal anesthesia. In Case 1 death ensued 20 days after anesthesia, and neuropathological examination revealed edema of the meninges, myelinosis of the lower cord, and extensive degeneration of the fibers of some small nerve roots, with loss of myelin sheaths.

Brock, Bell, and Davison [6] (Case 7) report on a patient who developed flaccid paraplegia in flexion and a sensory level at the 12th thoracic dermatome three days postoperatively. The patient died three months later, and the spinal cord was examined pathologically. There was an extensive destruction of myelin sheaths, axis cylinders, and glia, mostly at the periphery of the cord and at the zones of entrance of the posterior roots.

Brain and Russell [7] report the case of a 33-year-old man who died three months after spinal anesthesia. This patient showed massive softening of the lower thoracic and upper lumbar cord with focal demyelination. There was involvement of blood vessels, especially of the pia, with partial or complete hyaline necrosis. Meningitis was limited to an uneven, mainly perivascular infiltration with lymphocytes, monocytes, and a moderate number of neutrophilic and eosinophilic leucocytes.

Kamman and Baker [8] report a case of a patient who developed flaccid paraplegia two days after spinal anesthesia and died seven months later. Their findings demonstrated in the cervical area myelin changes in the columns of Goll and swelling and chromatolysis of the anterior horn cells. In the upper thoracic area, there were swelling of the anterior horn cells and thickening and fusion of the leptomeninges, more extensive posteriorly than anteriorly. In the mid-dorsal area, there were scattered petechiae in the gray matter, and the subarachnoid and subdural spaces were replaced by a softened area; there were large areas of hemorrhage and severely damaged anterior horn cells. In the upper lumbar area, the posterior columns were almost completely destroyed; the anterior horn cells were swollen and rounded,

showing complete chromatolysis, and laterally and posteriorly the entire subarachnoid and subdural spaces were replaced by an acellular membrane infiltrated with mononuclear cells.

Woods and Franklin [9] report a case in which symptoms came on immediately after spinal anesthesia, resulting in relentless progression and the production of a sensory level at the sixth thoracic dermatome and a spastic paraplegia. A laminectomy was performed because of adhesive arachnoiditis, demonstrated myelographically. The patient died four days postoperatively. Pathological examination of the spinal cord revealed a dense, grayish-white, avascular, plastic exudate surrounding the cord and cauda equina, extending from the cervical-thoracic junction caudally. The cauda was adherent to the thickened overlying dura. Many small cystic pockets, containing gelatinous yellow fluid, were observed posterior to the cord. Cross sections of the cervical cord showed degeneration of the columns of Goll and Burdach. Below the fourth thoracic segment there was demyelination of the posterior columns and periphery of the cord. The roots showed little demyelination or fragmentation of axis cylinders, in spite of pronounced adhesive arachnoiditis.

Winkelman [10] recently reported 11 cases in which a detergent was accidentally injected with the spinal anesthetic. Three of his cases terminated fatally, and in the remainder recovery was gradual over a period of months. Winkelman's Case 3 showed development of leg weakness, sphincteric disturbances, and a decrease in perianal sensation, coming on 11 days after spinal anesthesia. This patient showed sensorial clouding and flaccid paraplegia, and death occurred 34 days after development of his leg symptoms. The spinal cord showed no gross abnormalities. Microscopically, there were a marginal status spongiosus and degenerative changes in the anterior and posterior roots, which were more marked in the lower cord. The pia was thickened, fibrotic, and adherent to the undersurface of the dura and to the cord margins. The subarachnoid space was obliterated in places, especially in relation to the posterior aspect of the cord. Areas of demyelination were seen in the posterior and lateral columns of the cord, especially in the thoracic region.

The present case is the eighth pathologically verified case of adhesive arachnoiditis reported in the literature. It differs from all the others in the fact that the entire neuraxis was involved in a progressive process with onset 24 to 48 hours after spinal anesthesia. The patient's first clinical manifestations were those of paralysis of the bladder, followed by leg and chest pain, which may well have been due to posterior root irritation concomitant with development of the adhesive arachnoiditis. The patient developed a profound organic mental syndrome and death ensued 63 days after spinal anesthesia.

PATHOGENESIS OF ADHESIVE ARACHNOIDITIS FOLLOWING SPINAL ANESTHESIA

Numerous causes regarding the etiology of post-spinal-anesthesia arachnoiditis have been advanced.

Davis and associates,[11] basing their opinion on intrathecal injection of comparable doses of human anesthetic agents—Spinocain and Gravocain (solutions of procaine and strychnine) and procaine (Scurocain)—found a constant neurological reaction, consisting of inflammation of the arachnoid with thickening of the membrane and collection of proliferated arachnoidal cells and plasma cells in the membrane. This reaction was most marked in the lumbar and sacral segments, gradually diminishing

Data in Verified Cases of Adhesive Arachnoiditis

Author	Anesthetic Agent	Onset	Duration of Symptoms at Death	Neuropathological Findings		
				Brain	Meninges	Spinal Cord
Lindemulder [8] Case 1	1.5 cc. of Apothesine	Not listed	20 days	Congestion and edema of brain substance; numerous false psammoma bodies of myelin droplet type in pons and medulla	Congestion and numerous small psammoma bodies	Congestion
Case 2	Same agent	Not listed	12 days	Not reported	Edema of meninges	Myelinosis of lower cord, especially near meninges; extensive degeneration of fibers of some small nerve roots with loss of myelin sheaths
Brock, Bell, and Davison [6] Case 7	10 cc. of 1:500 solution of dibucaine	3 days	3 mo.	Not reported	Dura grossly intact; pia-arachnoid hyperemic	Demyelination, more marked at the periphery and in the lateral and posterior columns from Th9 to sacral segments; breakdown of axis cylinders, with swelling and corkscrew appearance of axones; chromatolysis, pigment atrophy, and vacuolation of ganglion cells
Brain and Russell [7]	Spinocain, 2 cc.	Back pain in 7 days; difficulty in walking in 30 days	112 days	Grossly normal	Grossly normal, but microscopy revealed partial or complete hyaline necrosis of pial blood vessels and sparse infiltration of meninges with lymphocytes and plasma cells	Softening Th12 to L2; opacity of posterior columns; necrosis of gray and white matter L3 to L5

Kamman and Baker [8]	First, 80 mg. piperocaine, then, 1 wk. later, 240 mg. piperocaine	Immediate after 2d anesthetic	7 mo.	Normal	Normal in cervical area, but in thoracic and lumbar areas leptomeninges thickened and fused posteriorly in acellular, fibrous membrane	Swollen myelin sheaths and finely granular myelin in columns of Goll in cervical cord; lower thoracic cord softened, with hemorrhage in lateral horns and demyelinated posterior columns; axis cylinders swollen and fragmented; neurones swollen and chromatolytic
Woods and Franklin [9]	Continuous procaine-tetracaine mixture	Immediate	5 mo.	Not reported	Adhesive pachymeningitis up to cervicothoracic junction with dense, grayish-white, avascular, plastic exudate over entire cord and cauda equina; many small cystic pockets containing gelatinous yellow fluid	Degeneration of posterior columns and, below Th4, demyelination of posterior columns and the cord periphery; cauda equina roots showed little demyelination or fragmentation of axis cylinders
Winkelman [10] Case 3	Spinal (agent not named)	"Within few days"	34 days	Not reported	Pia mater thickened, fibrotic, and adherent to undersurface of dura and cord margins; obliterated subarachnoid spaces, especially posteriorly	Marginal status spongiosus; areas of demyelination in posterior and lateral columns, especially in thoracic region; degenerative changes in anterior and posterior roots
Paddison and Alpers	Tetracaine hydrochloride with glucose	Immediate	63 days	Gross examination revealed marked basilar thickening of leptomeninges and marked dilatation of ventricles; microscopy revealed thickened leptomeninges and poorly stained ganglion cells, with attenuated processes and Nissl substance alteration	Dura adherent to cord substance; entire dorsolateral surface showing cloudy, thickened meninges, tightly adherent to cord parenchyma; microscopy revealed profound, proliferative adhesive arachnoiditis with sparse round-cell infiltration over entire brain stem and cord and enmeshing nerve roots	Demyelinated anterior and posterior nerve roots; demyelinated cord periphery; demyelinated fasciculus gracilis; pyknosis, loss of Nissl substance, and nuclear changes of anterior horn cells

through the thoracic and cervical segments. Myelin sheath stains revealed peripheral demyelination of the cord and nerve roots. Signs of retrograde degeneration of the anterior horn cells were also evident in Nissl stains.

Lundy and associates [12] felt that the neural changes were directly proportional to the concentration of the anesthetic drug. All dogs injected with 5 cc. of a 20 to 50% solution of drug developed permanent paralysis. Histological examination revealed demyelination of the periphery of the cord but no leptomeningeal involvement. The physical findings were corroborated in the cat by MacDonald and Watkins,[13] but no histological studies were made. They also felt that the additional common constituents of the anesthetic materials had no role in the neural damage.

Neurological complications of many sorts have been recorded following spinal anesthesia. Their cause appears not to have been definitely determined, and in the reported instances there seemed to be no relationship between the complications and the nature of the anesthetic or the type of anesthesia, whether single-dose or continuous. It seemed reasonable therefore to investigate other possibilities, of which the presence of a detergent as a source of arachnoiditis following spinal anesthesia appeared to be a possible cause. This has been suggested previously (Winkelman). In the case here reported the cleansing agent was a commercially available homogeneous blend of higher polyphosphates, carbonates, and patented organic wetting agents, consisting chiefly of hydrocarbon sulfonates. The detergent in question was found to be nonirritating to rabbit skin in a concentration of 10 gm. per gallon (2.6 gm. per liter) of water. One cubic centimeter (1 cc.) of a 2.5% solution, or 1.25 gm. of material, was fatal to a 20-gm. mouse.†

The relationship of the detergent to the arachnoiditis is conjectural, but it is possible that in sufficient concentration it is capable of causing the reaction described in the case here reported, either by direct action or by permitting increased neural toxicity of the anesthetic agent by surface activity. A number of observations bearing on the biological activity of surface agents are available and may shed light on the problem.

Loeb,[14] in 1913, found that surface-active agents, among them bile salts and higher fatty acids, when applied to the unfertilized sea urchin egg, produced cleavage and development, and that higher concentrations caused cytolysis. Mirsky [15] and Anson [16] suggested that the protein molecules of the cells may be disrupted by the pull of the detergents and thus denatured. Leopold,[17] in his experiments on the ocular effect of detergent materials instilled in the ocular sac of rabbits, concluded that detergents, particularly in high concentrations, are potentially toxic to external ocular structures, and that these agents should be used cautiously on the intact cornea and not be repeatedly used on the abraded cornea. Reiner [18] has found that the anionic surface-active compounds are potent agents in the production of venous thrombosis. The alkyl sulfates and sulfonates were found to produce a thrombus more readily than their straight-chain isomers. Orbach and Petretti [19] were able to demonstrate marked thrombogenic properties of sodium tetradecylsulfate. Hodges ‡ has found that Alconox used in the preparation of hematological laboratory glass-

† These data were furnished through the cooperation of Louis S. Zisman, Director of Research of Alconox, Inc.

‡ Hodges, John: Personal communication to the authors.

ware left a residual film with sufficient activity to nullify the validity of fragility tests, owing to increased hemolysis of normal erythrocytes by the residual detergent.

Lisi,[20] in frog heart perfusion experiments, found that anionic, cationic, and nonionic surface-active compounds were toxic to that organ in the range of 0.0001 to 0.002% solutions. For comparison, potassium dichromate had a comparable toxicity of 0.01 to 0.02%. Lisi states that the most toxic agents produced effects upon the heart without markedly altering the surface tension of the solution employed.

Höber [21] found that commonly used detergents have a poisonous effect upon frog muscle, due to the fact that the nonpolar organophilic half of the ion is built up by a long chain of alkyl radicals (8 to 18 carbon atoms), the polar hydrophilic half of a sulfonate or sulfate. If brought into contact with the organic surface membrane of a cell, this structure, owing to the strong attachment of the alkyl chains to its surface, and owing to the pull of the hydrophilic part toward the surrounding water, is subjected to a heavy stress, terminating in tearing the membrane to pieces (by denaturing and loosening the membrane components—bacteriolysis, cytolysis).

Since we found such a severe case of adhesive arachnoiditis, in which a hitherto largely unrecognized agent, a detergent, was inadvertently injected into the subarachnoid space, we have attempted to demonstrate that the detergent materials have a profound biological activity even when their presence is not detectable by surface-tension measurements upon the solutions employed.[21] The concentration of the detergent material in this case is purely conjectural, but from the demonstrated biological activity of detergent materials we hypothesize that the detergent introduced in this case may have had a specific neurotoxic potentiality or that its surface activity allowed the anesthetic agent to exert an increased neural toxicity.

SUMMARY

The case here reported represents a severe, extensive, fatal case of adhesive arachnoiditis following spinal anesthesia. It was found that a hitherto not widely recognized agent, a detergent, was inadvertently introduced intrathecally during the anesthesia. It is possible that this detergent substance, owing either to its inherent biological activity or to its synergistic activity with the anesthetic agent, produced this severe damage to the neural structures.

An attempt has been made to show that detergent compounds have a profound biological activity and that some residual surface-active agent remains even on well-rinsed laboratory glassware.

It is immediately evident that caution should be exercised in the use of detergent-cleaned apparatus for intrathecal injections, and that detergent materials should probably not be employed in the preparation of those items used in mixing and injecting spinal anesthetic agents.

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EVALUATION OF SEIZURES IN THE ADULT

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THE GENERALIZATION that every adult patient who develops a seizure disorder should have an air encephalogram is commonly accepted.* Yet the search for expanding intracranial lesions by this method is frequently disappointing, and the procedure is not without risk.

Seizures may be an initial symptom in 20 to 35% of patients with intracranial tumor. On the other hand, among large groups of patients with seizure disorders the number of brain tumors demonstrable by air encephalography varied from 1%, in the younger patients, to 10%, in the older patients.[7] Because of the serious implication of seizures developing in the adult, it is important that diagnostic methods be sufficiently accurate to indicate the presence or absence of intracranial mass lesions and that these methods be put in proper perspective with regard to their usefulness and benignancy.

PRESENT INVESTIGATION

All patients who have been admitted because of seizures to the Second (Cornell) Neurological Service, Bellevue Hospital, and the New York Hospital during the past 10 years have been reviewed to establish the usefulness and the place of diagnostic methods employed in these institutions in evaluating the significance of seizures.

The material for this study includes 245 patients whose seizures began after the age of 12 years. These patients were selected because a history of the illness was available, and physical and neurological examinations, skull x-rays, spinal fluid examinations, and encephalograms were made. Electroencephalograms were recorded on 215 of the group.

One hundred ninety patients in this series had generalized seizures (Chart 1). In 106 patients the seizures started after the age of 35, and in 84 patients they started before the age of 35. Forty-eight patients had generalized seizures beginning after the age of 35 and had normal neurological examinations, skull x-rays, and spinal fluid examinations, and an electroencephalogram not suggesting brain tumor. None of this group of patients had intracranial mass lesions demonstrable by air encephalography. Thirty-six showed normal ventricular systems, and 12 had cortical atrophy. The same results, except for the lower incidence of cortical atrophy, were noted in a similar group of 43 patients whose seizures began before 35 years

From the Second (Cornell) Neurological Service, Bellevue Hospital, and the Department of Medicine, New York Hospital, Cornell Medical Center.

* References 1 through 6.

of age. In one patient in this group who subsequently proved to have a brain tumor the neurological examination was positive before the second encephalogram was done.

Fifty-two patients with generalized seizures beginning after the age of 35 had evidence of focal brain dysfunction on neurological examination; many had abnormalities of skull x-rays or spinal fluid or had an electroencephalogram suggestive of neoplasm. Thirty-seven of these had mass lesions demonstrable on air encephalograms; 8 had cortical atrophy, and 7 had normal ventricular systems. Similar figures were obtained in a group of 22 patients with generalized seizures beginning before 35 years of age who had evidence of focal brain dysfunction on neurological examination.

		106 PATIENTS OVER 35			84 PATIENTS UNDER 35		
		NEUROL. EXAM. POS.	NEUROL. EXAM. EEG. CSF AND SKL. X-RAY NEG.	NEURO. EX. NEG. EEG. CSF AND/OR SKL. X-RAY POS.	NEUROL. EXAM. POS.	NEUROL. EXAM. EEG. CSF AND SKL. X-RAY NEG.	NEURO. EX. NEG. EEG. CSF AND/OR SKL. X-RAY POS.
AIR ENCEPHALOGRAM	EVIDENCE OF MASS LESION	37 BRAIN TMR. = 36 ABSC. = 1	0	1 BRAIN TMR. = 1	12 BRAIN TMR. = 11	0	0
	NO EVIDENCE OF MASS LESION	15 CORTICAL ATR. = 8	48 CORTICAL ATR. = 12	6 CORTICAL ATR. = 1	10 CORTICAL ATR. = 2	43 C.A. = 3 B.T. = 1*	18 C.A. = 4 B.T. = 2+ CYST = 1

* = LATER FOUND TO HAVE A BRAIN TUMOR
\+ = CALCIFICATION ON X-RAY BRAIN TUMOR AT OPERATION

Chart 1.—Generalized convulsions in 190 patients.

There were 25 patients with generalized seizures and negative neurological examinations, but with one or more abnormalities in the skull films or spinal fluid or a focal type of electroencephalogram. Of the seven in this group whose seizures began after 35 years of age, only one had evidence of a mass lesion on air encephalography. In this patient the electroencephalogram indicated the presence of a neoplasm and the spinal fluid protein was abnormally high. Of the 18 patients with seizures beginning before the age of 35, none had evidence of a mass lesion on air encephalography. Two had tumors suggested by calcification seen on routine skull x-rays: In one the tumor was confined to the bone; in the other a calcified spongioblastoma was found at operation, although pneumonencephalograms were negative.

Somewhat different results were obtained in the group of 55 patients whose seizures were focal in nature (Chart 2). Thirteen patients with focal seizures had negative neurological examinations, skull x-rays, and spinal fluid examinations, as well as electroencephalograms not suggestive of brain tumor. In the group of five

		34 PATIENTS OVER 35			21 PATIENTS UNDER 35		
		NEUROL. EXAM. POS.	NEUROL. EXAM. EEG. CSF. AND SKL. X-RAY NEG.	NEURO. EX. NEG. EEG. CSF. AND/OR SKL. X-RAY POS.	NEUROL. EXAM. POS.	NEUROL. EXAM. EEG. CSF. AND SKL. X-RAY NEG.	NEURO. EX. NEG. EEG. CSF. AND/OR SKL. X-RAY POS.
AIR ENCEPHALOGRAM	EVIDENCE OF MASS LESION	22 BRAIN TMR. = 21 ABSC. = 1	2 B.T. = 2	0	8 B.T. = 8	1 B.T. = 1	0
	NO EVIDENCE OF MASS LESION	5 CORTICAL ATR. = 3	3 C.A. = 2	2 C.A. = 1	2 C.A. = 1	7 C.A. = 1	3 B.T. = 1+

+ = LATER FOUND TO HAVE A BRAIN TUMOR

Chart 2.—Focal convulsions in 55 patients.

	FINAL DIAGNOSES		
	SUPRATENTORIAL MASS LESION	CORTICAL ATROPHY	NO STRUCTURAL LESION
FOCAL E.E.G. SUGGESTING NEOPLASM	49	1	2
ABNORMAL E.E.G.	14	29	74
NORMAL E.E.G.	8	8	28
TOTAL	71	38	104

TWO PATIENTS WITH POSTERIOR FOSSA TUMORS HAD ELECTROENCEPH'GRMS
THESE ARE EXCLUDED FROM THIS CHART

Chart 3.—Evaluation of the electroencephalogram in 215 patients with convulsions.

whose seizures began after 35 years of age, two had mass lesions demonstrable by air encephalography. Among the eight patients whose seizures began before the age of 35, one mass lesion was found.

Twenty-seven patients had focal seizures beginning at 35 years of age or after and had evidence of focal brain dysfunction on neurological examination, and many also had abnormalities in the skull x-ray or the spinal fluid; others had electroencephalograms suggestive of brain tumor. Twenty-two of these patients had mass lesions demonstrable by air encephalography. Of 10 patients with seizures beginning before the age of 35 and with similar findings, 8 had mass lesions.

A total of five patients in both age groups had focal seizures, negative neurological examinations, but one or more abnormalities in the skull x-rays and the spinal fluid, or had electroencephalograms suggesting neoplasm. There were no mass lesions demonstrable by air encephalography, but one patient later was found to have a tumor.

For 213 patients electroencephalograms were recorded (Chart 3). For 52 of this group they were interpreted as showing a neoplasm, and in 49, or 94%, a mass lesion was demonstrable both by air encephalography and at operation. There were three instances, or 6%, in which the records indicated the presence of a brain tumor which could not be demonstrated by air encephalography.

The 49 patients in whom the electroencephalogram suggested the presence of a neoplasm represent 70% of the total number (71) of proved supratentorial brain tumors. Of the remaining 22 patients, or 30%, 14, or 18%, had abnormal electroencephalograms not suggestive of neoplasm, and 8, or 11%, had normal electroencephalograms.

SUMMARY

Regardless of the type of seizure, the electroencephalogram rarely indicates the presence of an intracrainal mass lesion when there is a negative bedside neurological examination. Further, irrespective of the age of onset of generalized seizures, if the bedside neurological examination fails to indicate evidence of focal brain dysfunction, air encephalography at that moment is not likely to demonstrate a mass lesion. It may, however, reveal cortical atrophy. When subsequent and repeated bedside neurological examination first yields evidence of focal brain dysfunction, then air encephalography may indicate the presence and site of an intracranial mass lesion.

Regardless of the age of onset, if the seizures are focal, air encephalography is likely to indicate the presence of an intracranial mass lesion, despite a negative neurological examination.

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COMPLICATIONS FOLLOWING CEREBRAL ANGIOGRAPHY

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CEREBRAL angiography is an invaluable diagnostic method which has now been widely accepted. In certain vascular lesions the information thus afforded is not equaled by any other means; both the location and the nature of tumors are often disclosed with exactness. The introduction of the percutaneous method by Egas Moniz,[19] Loman and Myerson,[18] Turnbull,[25] Shimidzu,[23] and others has greatly extended its usefulness. The surgery of intracranial aneurysms has been furthered enormously. However, the enthusiastic reports dealing with its applicability have not always been tempered by that caution which is bred of remorse. It is to emphasize the dangers believed inherent in angiography and to suggest some contraindication to its use that this paper is written.

METHOD AND MATERIAL

A series of 234 consecutive carotid angiographies, performed upon 200 patients between 1947 and 1952, have been reviewed. In each instance the solution employed was 35% iodopyracet (Diodrast). The open method of carotid exposure was employed in 33 cases; the percutaneous, in the remainder, or 201.

The total amount of iodopyracet injected into each carotid artery varied from 10 to 60 cc.; however, in each injection 8 to 10 cc. of iodopyracet was used. The average amount injected in one sitting was 30 cc. An interval of four to six minutes elapsed between injections. The third injection, if necessary,was usually made 15 to 20 minutes later, providing no complications had been observed. To prevent clotting within the needle, frequent injections of small amounts of sodium citrate were made into the artery while the needle remained in situ. A sharp # 18 spinal needle was employed throughout.

Premedication consisted of morphine, ¼ grain (15 mg.), and atropine, $\frac{1}{100}$ grain (0.60 mg.), in 70% of the patients. In these the skin was infiltrated with 1% procaine hydrochloride. In the remaining 30% of these patients intravenous thiopental (Pentothal) sodium or nitrous oxide was employed. Small amounts of 1% procaine hydrochloride (2 to 25 cc.) were injected through the indwelling needle after the administration of iodopyracet in the hope of lessening arterial spasm. Occasionally the carotid sinus was also blocked with procaine before arteriography.

The patients ranged in age from 2 to 69 years; 89 were females and 111 males.

Read before the Section on Nervous and Mental Diseases at the 102d Annual Meeting of the American Medical Association, New York, June 2, 1953.

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COMPLICATIONS (TABLE 1)

Fatalities.—One death occurred which was unquestionably attributable to the injection of iodopyracet. In this instance the practice of limiting the total volume injected in one carotid to 30, or at the most 40, cc. was violated.

B. B. (A. H. # B4569), a 7-year-old boy, was admitted because of enlargement of the head, which had become evident shortly after birth. The skull circumference was 53 cm. A soft, round mass, 3 to 4 cm. in diameter, was present in the left temporal region. A loud systolic murmur was audible over it. The occipital, as well as the superficial temporal, arteries were very prominent on the left side, and murmurs were heard over both these regions. The left pupil was larger than the right. No other neurological abnormality was observed. The electrocardiogram was normal.

A sensitivity test for iodopyracet was negative. Open left common carotid arteriography was performed with 1/200 grain (0.30 mg.) of atropine, under general anesthesia, which was commenced with vinyl ether (Vinethene), followed by nitrous oxide and, eventually, by open-drop ether. Six injections of 10 cc. of 35% iodopyracet were carried out within 40 minutes, some technical difficulties with the x-ray machine having vitiated the first four of these efforts. Within five minutes after the last injection, respirations suddenly ceased. The pulse was obtainable for another five minutes, during which time 7½ grains (0.50 gm.) of caffeine and sodium benzoate and two injections of 0.5 cc. of 1:1,000 epinephrine hydrochloride were administered by intracardiac injection. At the end of this time the heart beat had ceased. Autopsy revealed (1) arteriovenous aneurysm, between the left middle meningeal artery and the veins of Labbé, and (2) marked edema of the brain and congestion of the blood vessels therein.

TABLE 1.—*Complications of Cerebral Angiography*

Diagnosis	No. Patients	Deaths: Due to Angiog.	Deaths: Hastened by Angiog.	Survival Time	Permanent Hemiplegia	Transient Hemiplegia	Other Complications
Brain tumors	54	..	1	24 hr.	..	6	.....
Aneurysms	37	1		5 min.			
			1	48 hr.	2	4	.....
Subarachnoid hemorrhages presumed due to aneurysm.	29	..	..	.....	1	3	1 neck hematoma 1 scotoma
Cerebral thrombosis, embolisms, or hemorrhages due to atherosclerosis	17	..	1	6 hr.	.	2	.....
			1	33 hr.			
			1	6 days			
			1	8 days			
Cephalalgias of unknown origin	16	..	..	.....	..	..	1 facial weakness
Head injuries	13	..	..	.....	..	2	.....
Miscellaneous	13	..	..	.....	..	1	1 neck hematoma 1 transient numbness
Convulsive disorders	21	..	..	.....	..	1	3 transient numbness
Total	200	1	6	.....	3	19	8 = 37 cases

Comment.—Because of technical difficulties, the first roentgenograms were unsatisfactory. Since the patient's condition was seemingly unchanged, the physician carrying out the angiography made the grievous error of essaying another pair of stereoscopic pictures. Even in an adult this should have been postponed; in a child the amount of iodopyracet tolerated is probably far less.

Fatalities were seemingly hastened by arteriography in six patients who entered the hospital in terminal stages of their illnesses. Four suffered from extensive

arteriosclerotic thromboses; one, from rupture of a berry aneurysm of the vertebral artery, and one, from multiple metastases originating in a carcinoma of the bronchus. Brief abstracts of these cases follow.

CASE 1.—J. B. (A. H. # B17564), a 57-year-old white man, gave a history of sudden onset of left-sided hemiplegia five weeks previously. Vision was said to have been lost for two days, with subsequent recovery. He had had severe headache for two weeks prior to admission. Examination revealed a well-oriented white man, with complete flaccid paralysis of the left lower face, arm, and leg. The stretch reflexes were hyperactive on the left; plantar response was strongly extensor on that side. The electrocardiogram showed old posterior wall myocardial infarction.

Percutaneous right common carotid arteriography was performed with the use of four 10 cc. injections of 35% iodopyracet (under ¼ grain of morphine premedication and local infiltration of the skin). There was no filling of the right internal carotid artery in these films. Apnea for 30 seconds followed immediately after the last injection. The blood pressure fell from 120/80 to 80/40, and he became comatose. Cheyne-Stokes respirations followed the intravenous administration of 7½ grains of caffeine and sodium benzoate, however; and he regained consciousness. He expired 33 hours after performance of the angiography. Autopsy revealed (1) thrombosis of the right middle cerebral and basilar arteries with recent encephalomalacia involving the right frontal and parietal lobes, and (2) moderate atherosclerosis of the coronary arteries and an old healed infarction of the posterior wall of the left myocardium.

CASE 2.—L. D. N. (A. H. # B9002), a 45-year-old white woman, was admitted in semicoma. Three weeks previously she had begun to experience severe headaches and to become drowsy. She vomited continuously for three days before admission and was reported to have lapsed into stupor a few hours after lumbar puncture. T. 99; P. 80; R. 20; B. P. 130/90. She comprehended the words spoken to her but was unable to speak. Her left pupil was in full dilation; right pupil, in mid-dilation, and neither reacted to light. She moved all four limbs, but there was slight right hemiparesis. The reflexes were essentially normal. A closed carotid angiogram was performed on the left side with three injections of 10 cc. of 35% iodopyracet (under 200 mg. of intravenous thiopental sodium anesthesia). The angiogram was normal save for slight displacement of the left anterior cerebral artery downward. She became incontinent of stool and urine after the last injection of the dye and appeared to be in deep coma. One hour later bilateral occipital trephination was performed and a ventriculogram obtained. This was interpreted as normal.

Consciousness was never regained after angiography. Her condition slowly deteriorated, and she expired in respiratory failure eight days later. Autopsy revealed (1) moderate arteriosclerosis of the cerebral arteries; (2) marked encephalomalacia of the left parietal lobe and moderate diffuse congestion of the brain, and (3) a moderate cerebellar pressure cone.

CASE 3.—M. E. Q. (A. H. # B1200), a 42-year-old white woman, suffered a sudden sharp pain in the back of the neck, followed immediately by loss of consciousness, 10 days prior to admission. A lumbar tap, performed in another hospital after her regaining consciousness, disclosed grossly bloody fluid. Prior to arteriography the patient was aphasic and semistuporous. There were bilateral papilledema of 0.5 D., moderate stiffness of the neck, slight lower right facial weakness, marked hemiparesis on the right side, and slight hemiparesis on the left side. There was generalized areflexia with exception of minimal knee and ankle jerks on the right. B. P. 160/120.

Three 10 cc. injections of 35% iodopyracet solution were made into the left common carotid artery by percutaneous technique (with $\frac{1}{150}$ grain [0.40 mg.] of atropine premedication and local infiltration of the skin). The arteriogram disclosed no aneurysm. She became deeply comatose one-half hour after the last injection, moved her left arm and leg but slightly, and expired in respiratory failure 48 hours later. Autopsy revealed (1) saccular aneurysm of the right vertebral artery with diffuse subarachnoid hemorrhage about the base of the brain, (2) marked edema of the brain, and (3) congenital atresia of the left posterior communicating artery.

CASE 4.—S. M. C. (A. H. # B8741), a 46-year-old electrician, was admitted because of severe headache, of two weeks' duration; dizziness, of four days' duration, and sudden onset of loss of consciousness with left hemiplegia, of 12 hours' duration. He was comatose on admission; the

eyegrounds were normal. All extremities were moved on painful stimulation. The stretch reflexes were hyperactive throughout, and the plantar response was extensor bilaterally. No other neurological changes were observed.

Open right common carotid arteriography was performed with the use of three 10 cc. injections of 35% iodopyracet (under 1/100 grain [0.60 mg.] of atropine premedication and 625 mg. of intravenous thiopental sodium anesthesia). Roentgenograms disclosed a normal vascular tree. His condition rapidly deteriorated after arteriography, and he expired within six hours. Autopsy revealed (1) recent thrombosis of the basilar artery with extensive encephalomalacia of the pons and right and left parietal cortices, and (2) moderate arteriosclerosis of the cerebral arteries.

Case 5.—H. M. (A. H. # B29627), a 60-year-old man, had been known to be hypertensive for many years and had begun to experience episodes of forgetfulness one year previously. Weakness of the legs became apparent three months prior to admission. He became suddenly comatose one day before admission. Admission B. P. 230/135; P. 84; R. 24; T. 100 F. The neck was rigid; he was in coma, but he moved his extremities on pain. There was hyperreflexia bilaterally. The plantar response was flexor bilaterally. Lumbar puncture disclosed xanthochromic spinal fluid, under normal pressure.

Left common carotid arteriography was performed by the percutaneous method; three 10 cc. injections of 35% iodopyracet solution were made. Immediately after the third injection the patient developed Cheyne-Stokes respirations and vomited. Right-sided hemiplegia appeared immediately; this cleared but slightly within the next six days. However, his condition continued to deteriorate, and he expired six days after arteriography. Permission for autopsy was not obtained.

Case 6.—E. O. T. (A. H. # A90064), a 58-year-old mason, was admitted because of mental confusion and left-sided convulsions. He was comatose and moved the right, but not the left, side on painful stimulation. There was early papilledema bilaterally. Stretch reflexes were hypoactive on the left. The plantar response was extensor on the left.

An x-ray of the chest disclosed an area of increased density in the left upper field. Right common carotid arteriography was performed by the percutaneous route with the use of three 10 cc. injections of 35% iodopyracet solution. Roentgenograms disclosed a space-occupying lesion in the left frontal region. His condition rapidly deteriorated after the last injection, and he expired two days later. Autopsy revealed bronchogenic carcinoma, anaplastic, of the upper lobe of the left lung, with multiple metastases to the brain; these were located in the left frontal lobe, in both parietal lobes, and in the cerebellum. There was diffuse generalized edema of the brain.

Hemiplegia.—Three patients developed permanent weakness of the opposite side after angiography; two of these had exhibited mild hemiparesis prior to the injections. While all had suffered recent subarachnoid hemorrhage from aneurysms of the carotid tree, there was little clinical evidence that further bleeding was responsible for the hemiplegia. In two cases the weakness appeared immediately after the last four 10 cc. injections, while in the third it became evident three hours later.

Transient hemiplegia or hemiparesis occurred after 19 of the 234 carotid angiographies (Table 1). The diagnoses for these patients were as follows: brain tumor, six; cerebral contusion, one; subdural hematoma, two; convulsive disorder, one; berry or arteriovenous aneurysm, nine. Ten had no preinjection neurological deficits. On the average, four injections of 8 to 10 cc. 35% iodopyracet were made in each patient, although one patient became hemiplegic after a single injection.

Contralateral sensory changes appeared immediately after angiography in six patients, lasting one to four hours. Recovery was complete in each instance. Most of these would probably have been overlooked had the procedure not been carried out under local anesthesia.

Neck hematoma of sufficient magnitude to require evacuation occurred in two patients. Prompt recovery followed in each instance.

Occlusion of branches of a retinal artery occurred in one patient. These changes were observed early and were serially recorded by retinal photographs. Since the retina is in reality a part of the brain, the scattered emboli or thrombi and the surrounding edema afforded a visible demonstration of the process as it probably occurred in the sensory motor cortex, and which was responsible for the transient monoparesis.

M. Z. (A. H. # B28342), a 44-year-old plasterer, was admitted because of severe occipital headaches of four weeks' duration. Physical examination disclosed no abnormalities on admission. His blood pressure was 116/64. He suffered transient weakness and numbness of the left arm

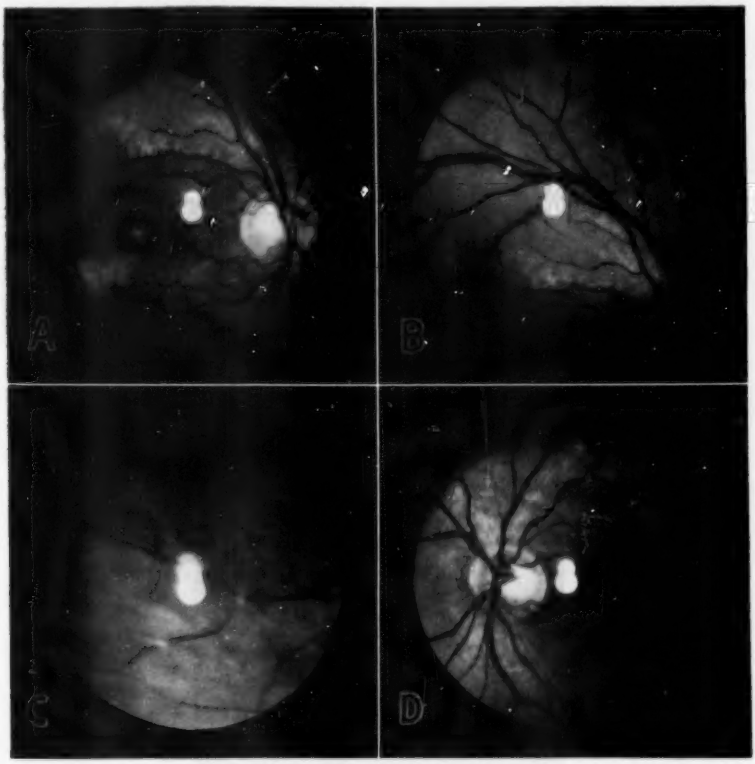

Fig. 1.—*A*, right eye 24 hours after injection, showing the two large ischemic area. *B*, same eye as that in *A*, with a more detailed view of the superior temporal area. *C*, temporal side, right eye, showing occlusions in a temporal area; *D*, left eye at time of original examination; sharp detail of disk with negative vessels.

following the third intracarotid injection of 10 cc. of iodopyracet. Five cubic centimeters of 1% procaine hydrochloride was injected into the right carotid artery, and the right stellate ganglion was blocked immediately with 1% procaine hydrochloride. The left monoparesis cleared in approximately two hours.

He did not complain of difficulty in seeing until the next morning. This he described as a slight blurring in the right eye and a shadow downward and to the left of his line of vision. On further questioning, he recalled that he had first noticed the shadow about an hour after angiography the previous day. This corresponded with the right inferior nasal quadrant field defect subsequently demonstrated.

Twenty-four hours later, when the first photograph was taken, the right disk was clearly outlined with a small central excavation and broad, peripapillary zone of retinal edema (Fig. 1*A*). The region supplied by the superior temporal artery, a broad triangle with the apex at the disk edge, was ischemic and milky-white (Fig. 1*B*). A small edematous area inferior to the macula was more than twice the disk diameter in length; its upper margin was flat and impinged upon the normal, pink macula. A small embolus was visible as a white line in one of the secondary branches of the superior temporal artery, and near the equator on the temporal side there were two similar occlusions (Fig. 1*C*).

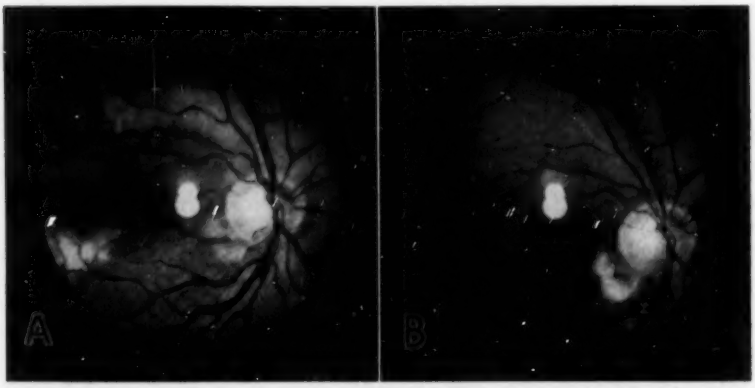

Fig. 2.—*A*, right eye three days later. Decrease in both areas of retinal edema; a fresh area of edema adjacent to the disk. *B*, right eye two weeks later. Almost complete absence of the large areas but increased thickness of the one close to the nerve head.

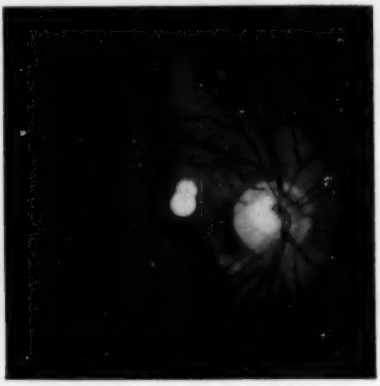

Fig. 3.—At the end of another month, 38 days after angiography, normal pink fundus, except for the fading spot near the disk.

The left eye was normal (Fig. 1*D*). The disk was clearly outlined, with a medium-sized central excavation. The veins and arteries were of normal caliber and distribution.

Three days later, there was a striking decrease in both areas of the retinal edema, with, however, a fresh oblique ischemic area, about ½ disk diameter long and about ¼ disk diameter wide, in opposition to the inferior temporal margin of the disk (Fig 2*A*).

After another two weeks, the large areas of retinal edema were thinner, but the oblong one was more elevated and so thick that it completely obscured the vessels in that region (Fig. 2*B*). The vision in the right eye was 20/40.

At the end of another month, the areas of papillary edema had entirely disappeared, and the pink color of the fundus was restored in all parts except the lower portion of the oblong area, which remained slightly hazy (Fig. 3). No emboli were visible, and the vision was 20/20. The visual field was larger but still concentrically contracted, with the greatest loss in the inferior nasal sector.

A similar case has been recorded by Weekers.[26]

COMMENT

That cerebral angiography by means of sodium iodide, Thorotrast, and iodopyracet is attended with some risk has been apparent from most recorded experi-

TABLE 2.—*Data from Various Papers on Cerebral Angiography*

Authors	Total No. of Cases Reported	Diodrast, %	Maximum Amt. Diodrast Used in One Series, Cc.	Deaths	Permanent Hemiplegias	Transient Hemiplegias	Convulsions	Other Complications	Total No. of Complications
Abbott and others [1]	150	35 70	60	4 1	4	7	1	.....	17
Bull [5]	1,000	35	Not given	2	0	0	0	.....	2
Chusid and others [6]	Not given	35	50	0	0	2	0	.....	2
Curtis [7]	No. not given; 720 injections	35	120	1	0	0	4	Neck hematoma, 1	5
Dunsmore and others [8]	108	35	80	3	4	2	2	Carotid thrombosis, 1 Allergic reactions, 1 Injury to sympathetic chain, 1	14
Dyke and others [9]	3	70	35	0	0	1	0	Thrombosis of common carotid artery, 1	2
Enceset [11]	100	35	52	2	0	0	0	.....	2
Green and Arana [13]	107	35	Not given	0	0	0	0	Allergic reactions, 4 Transient aggravation of symptoms, 2	6
Gross [14]	10	70	30	0	1	0	3	.....	4
Ingraham and Cobb [16]	25	35	Not given	0	0	0	0	.....	0
Lindgren [17]	153	50 35	Not given	0	0	0	0	.....	0
Pool and Alexander [21]	9	35	40	0	0	0	0	.....	0
Radner [22]	221 Vertebral only	35	50	3	0	1	0	.....	4
Torkildsen [24]	2,000 Vertebral and carotid	35 50	Not given	Not given	Not given	Not given	Not given	.....	Not given

ences. In Table 2 are listed a number of the important papers which have dealt with this problem. In certain of these writings the inherent dangers are clearly stressed.

Concerning the factors responsible for the neurological complications of iodopyracet angiography (exclusive of neck hematoma) a number of valuable studies are available.

Curtis [7] suggested that "clot embolus" is a not infrequent cause of hemiplegia and recommends that the lumen of the needle be siliconed to prevent clotting. Abbott and associates [1] recorded an instance in which they believed that the sudden increase in intravascular pressure attendant upon the injection was responsible for fatal rupture of an aneurysm. In other patients they believed that hemiparesis resulted from alteration in the blood-brain barrier, as suggested by Olsson.*

* References 4 and 20.

The toxicity of iodopyracet was studied in monkeys by Foltz and associates.[12] They concluded that there were two effects upon the brain: "(1) a direct toxic action on the nerve cells; and (2) a protective vasospasm minimizing the amount of toxic substance reaching the nerve cells in any given period of time." In a similar study, Bloor and associates[2] observed the severe alteration of the permeability of the vessels in the brain of Macacus rhesus monkeys when injected with 50 or 75% solutions of iodopyracet. There was also progressive edema consequent upon the changes in the vascular walls.

Vasospasm of the surface vessels of the brain following intracarotid injections of iodopyracet was recorded by Holm[15] and others.† Broman and Olsson‡ confirmed these observations and stated that damage would be greatly increased if subsequent injections were made at less than 15-minute intervals. Our own observations demonstrate that vascular occlusion by embolus or thrombus is one cause of neurodysfunction.

SUMMARY

1. In a series of 234 consecutive carotid angiographic studies with 35% iodopyracet (Diodrast) there were 37 complications.

2. One of these was a fatality clearly due to the use of an excessive amount of the medium.

3. Death was seemingly hastened in six persons whose diseases had already rendered their demises imminent.

4. Three permanent hemiplegias occurred which appeared to have resulted from the procedure.

5. Nineteen transient hemiplegias or hemipareses were observed, also apparently due to iodopyracet angiography.

6. Contralateral sensory changes of a transient nature occurred in six patients.

7. One instance of retinal artery partial occlusion occurred and was recorded by serial retinal photographs.

CONCLUSIONS

1. Cerebral angiography carries a definite hazard. This is a calculable risk, which the information thus attainable may or may not justify.

2. If the information necessary for therapy is obtainable by methods which entail less risk, then the subjection of the patient to this added risk is not justifiable.

3. The development of a safer substance than iodopyracet (Diodrast) is urgently needed.

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ABSTRACT OF DISCUSSION

DR. A. EARL WALKER, Baltimore: It is indeed unfortunate that angiography, which I think is probably the most informative of technical diagnostic procedures in neurosurgery, should have a calculated risk, such as has been presented this afternoon. But that is the experience of everyone who has carried out this procedure.

In the Johns Hopkins Hospital, in the first 300 angiograms, our complications were approximately 4%. In the last 500 cases the complication rate has been 4.6%. We have had a certain

number of deaths, which have occurred from a few hours to a week or so after the procedure; these we believe are not complications, but are due to the primary disease for which the procedure was carried out. These occurred, in some 10 instances, in patients comatose from subarachnoid hemorrhage due to rupture of an aneurysm or an intracerebral hematoma. In four instances the patient had neoplastic or traumatic disease of the brain and subsequent to angiography was operated on and died.

We have had the same transient hemiplegias as Dr. Campbell; in fact, 10 of the patients in our series had such a complication. We have had no permanent hemiplegias. We have had four convulsive seizures, which occurred, however, in patients who had previously had convulsions. We have had two hematomas in the neck which gave trouble.

In assessing the etiological factors, we have not been impressed with spasm of the intracranial arteries, which we have not been able to demonstrate in animal experimentation; in fact, using iodopyracet or Thorotrast in monkeys and in cats, we have never been able to demonstrate spasm of the vessels. We have noted, when high concentrations of iodopyracet are used, that there may be increased permeability of the cerebral vessels; but that has occurred only when 70%, not 35%, iodopyracet was used. However, that may be one factor in the production of complications.

We have noted in experimental animals—and we think it may be rather important in clinical cases—that air emboli will cause stasis in the intracerebral vessels and the pial vessels, not only of the embolus itself, but of the material preceding and following it, which in this case is iodopyracet and which I think, when remaining in the brain, may produce toxic changes in the vessel and give rise to the neurological complications.

Our therapeutic techniques for relief of these complications have been somewhat successful. For the visual changes we have repeatedly injected the stellate ganglia, with improvement of vision. In the two cases in which such complications were present, the vision returned within 24 hours after blockage of the stellate ganglia. We have noted rather dramatic changes of the hemiplegia after blocking the stellate ganglion.

On the other hand, a preliminary block of the stellate ganglia before angiography has not changed the rate of complications. In a series of some 60 or 75 cases the complication rate was precisely the same as though the stellate ganglia were not blocked.

One other fact should be kept in mind, namely, that when the patient is under general anesthesia, one cannot tell whether he has had a reaction. With local anesthesia, one can have the patient talk and squeeze one's hand to determine whether there is any weakness. But if one has a patient under general anesthesia, a reaction may occur without anyone's suspecting it, and the subsequent injection of iodopyracet, which may aggravate the reaction, may be responsible for a fatality.

I would particularly emphasize that bilateral angiography, with the patient under general anesthesia, is apt to be associated with complications and death. We believe the risk is due to the fact that an unrecognized hemiplegia on the first side may be further complicated by a hemiplegia on the second side, with subsequent death.

I think it may be possible, by taking precautions, to decrease the incidence of complications in angiography; and, because we do believe that angiography is so informative, we should like to continue its use as much as possible.

DR. JOHN P. GALLAGHER, Washington, D. C.: Dr. Campbell has brought out the serious complications which may follow carotid angiography.

Many investigators have laid emphasis on the irritative or toxic effects of the contrast medium when it is brought into contact with a major artery. However, I believe that too little has been said regarding the possible pathologic consequences associated with the entrance of the needle into the vessel. Those who have exposed the femoral artery know how frequently this vessel may go into severe and prolonged spasm when it is stimulated with the tip of the needle at the moment the artery is pierced. The possibility of a similar reaction occurring during injection of the common carotid artery should not be overlooked in explaining some of the serious effects in the brain following carotid angiography.

Without question, the method of percutaneous injection of the carotid is more convenient and, when things go right, is much swifter than is that of open exposure of the vessel. In our hands, the complications have occurred with the use of the percutaneous method when multiple injections became necessary or when difficulty arose in gaining entrance into the artery with the probing

needle. One can only speculate whether arterial spasm or damage to the walls of the artery occurred under these circumstances, with clot formation and possibly embolic or thrombotic phenomena.

However, it must be admitted that there are dangers associated with either method of injection of the carotid artery. It should be remembered that carotid angiography yields important information which cannot be secured by any other means. Patients on whom this procedure is carried out are either actually or potentially in danger, by virtue of the presence of some intracranial lesion.

When all is said and done, the risks inherent in carotid angiography are only a portion of the risks assumed by the surgeon in treating such a patient.

DR. ELDRIDGE CAMPBELL, Albany, N. Y.: I wish to thank the discussants and to point out that the accuracy of a calculation of risk is proportional to the completeness and reliability of the basic figures accepted. In our series most angiographies were made under local anesthesia; early transient weakness or numbness thus became evident. Had these immediate observations not been possible, the number of "complications" reported today would have been materially less.

I wish I knew the values of stellate block. We employ it for such complications as have been mentioned but find it difficult to be sure how much it has contributed to the recoveries.

Concerning multiple punctures and multiple injections, it might be added that in our series one hemiplegia came on immediately after a single injection of 8 cc. of iodopyracet.

CREATINE METABOLISM IN PARALYSES DUE TO VARIOUS CAUSES, ESPECIALLY INJURIES TO THE SPINAL CORD

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CREATINE intolerance is characteristic of the various types of muscular dystrophies.* However, it has been described in many other conditions. Among the neurological diseases it has been noted chiefly in progressive muscular atrophy † and anterior poliomyelitis.‡ Of great importance is its occurrence both in acute anterior poliomyelitis and in the severe residuals. It has been reported in many non-neurological disorders but from few observations, as in immobilization [11] and amputation.[12]

Among the patients with injuries to the spinal cord were many with disturbances in metabolism of heat, water, sugar, etc. As a part of the studies of disturbances in metabolism there was included one on creatine tolerance.

The clinical material consisted of 14 patients with severe hemiplegia and 3 with crural paraplegia of cerebral origin, 9 patients who had been submitted to an anterior rhizotomy, and 6 patients with severe residuals of anterior poliomyelitis. This portion of the material was used to compare creatine metabolism in cases of paralysis due to upper motor neurone lesions with that in cases due to lower motor neurone lesions. The conclusions drawn from this study contributed to our deductions relating to injuries to the spinal cord at various levels. Of these there were 9 patients with injuries to the cervical spinal cord, 17 patients with uncomplicated injuries to the midthoracic and upper thoracic spinal cord, and 11 patients with injuries to the lower thoracic and lumbar portions of the spinal cord, both complicated by injury to the cauda equina. In all it was our opinion that the injury produced a complete physiological interruption of function, and in some an anatomical section was present.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion of policy of the Veterans Administration.

* References 1, 2, 3, and 4.

† References 5, 6, and 7.

‡ References 8, 9, and 10.

All patients were on a meat-free diet for two days prior to the test and throughout its duration. The test dose of creatine was 1 gm.

Creatine in the urine was determined by the Jaffe reaction. Creatine intolerance was found in many cases of injuries of the spinal cord and cauda equina. This intolerance was reflected either by a low percent of retention of creatine or a high amount of excretion during some 24-hour period of a 72-hour test. To determine whether the intolerance resulted from paralyses, 14 patients with very severe hemiplegia and 3 patients with crural paraplegia of cerebral origin were studied. There was no increase above the quantity usually given as the normal excretion for 24 hours (250 mg.). In only one case was there a slight diminution in percentage of

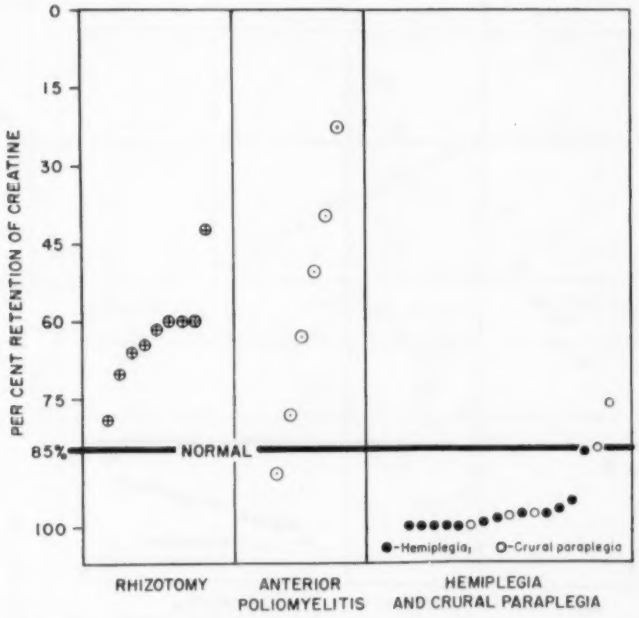

Chart 1.—Percent retention of creatine in patients with rhizotomy, anterior poliomyelitis, hemiplegia, and crural paraplegia.

creatine retention, a little less than the 85% or more said to be normal (Chart 1). Such paralyses as occurred as the result of an upper motor neurone lesion were not associated with creatine intolerance.

We then studied the cases with lower motor neurone paralysis (Chart 2). Creatine intolerance was found in all of the nine patients who had submitted to an anterior rhizotomy, the amount excreted ranging up to 790 mg. It was also present in six patients with widespread residuals of anterior poliomyelitis, the amount excreted ranging from 300 to 1,100 mg.

The level of injury to the spinal cord was then compared with the occurrence of creatine intolerance (Chart 3). It was found that creatine intolerance was present in all of the nine patients with injury to the cervical spinal cord, the amount excreted ranging from 325 to 800 mg.; it occurred in all of the 11 patients with

injuries to the lumbar spinal cord, the amount excreted ranging from 260 to 975 mg. In both of these groups injury to the spinal cord was complicated by concomitant injury to anterior roots or peripheral nerves. On the other hand, in injuries to the thoracic spinal cord, uncomplicated by injuries to widespread roots, creatine intolerance was found in none of the 17 cases, the amount excreted ranging from 60 to 240 mg. (Chart 4). Some of the disturbances of metabolic function in injuries to the spinal cord resulted from failure of impulses from the upper levels, such as the hypothalamus, to reach the part of the spinal cord necessary for that function. Here, however, since creatine intolerance, in injuries to the spinal cord, was found only when the condition was complicated by root or plexus injury, in the case of injury to the cervical spinal cord, and to the cauda equina, in injury of

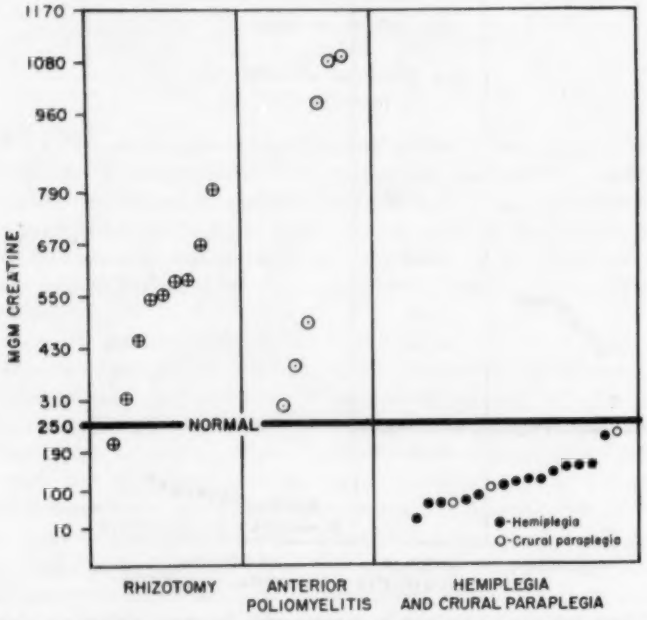

Chart 2.—Highest creatine excretion in 24 hours during a 72-hour period in patients with rhizotomy, anterior poliomyelitis, hemiplegia, and crural paraplegia.

lower thoracic and lumbar spinal cord, and since it was not found in uncomplicated lesions of the thoracic spinal cord, it seemed that creatine intolerance was not the result of failure of impulses originating in the upper levels, such as the hypothalamus, to reach the paralyzed muscles. Nor was it the result of paralysis itself, since it was not found in severe hemiplegia or crural paraplegia of cerebral origin.

It was always found in patients with anterior rhizotomy and with residuals of poliomyelitis. Therefore it was suggested that creatine intolerance in the cases of injury to the spinal cord resulted from the disturbance in metabolism of muscles deprived of their lower motor neurone supply.

In four of the patients studied, amputations of the lower extremities had been performed for one or another reason. In one, both lower extremities had been

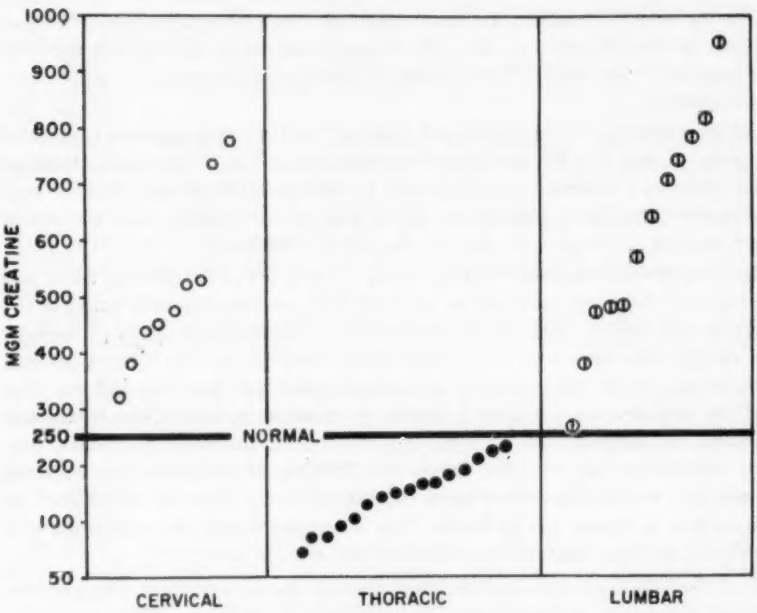

Chart 3.—Highest creatine excretion in 24 hours during a 72-hour period in spinal cord injuries.

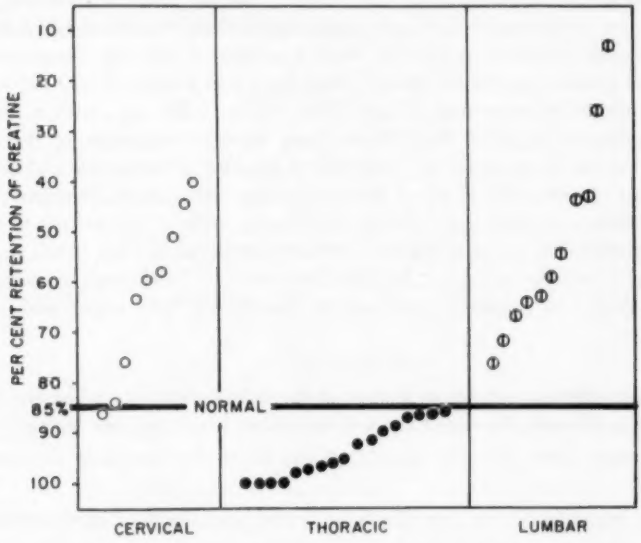

Chart 4.—Percent retention of creatine in spinal cord injuries.

amputated. In this case there was a lesion of the lower spinal cord and cauda equina. In the other three, but one lower extremity had been amputated, in cases with lesions at the 5th cervical, the 12th thoracic and cauda equina, and the 10th thoracic segment, respectively. These cases afforded an opportunity for some interesting speculations.

It had been reported by Cameron and Gibson [12] in 1922 that creatinuria resulted after amputation, and they felt that when the muscle mass is less than normal through any cause, there is a tendency to creatinuria. However, Milhorat and Wolff [13] suggested that the quantity of improperly functioning muscle, rather than the extent of muscle wasting, is responsible for the degree of creatinuria.

In the patient who sustained an amputation of both lower extremities there was a physiologically complete lesion at the level of T 12 combined with a lesion of the cauda equina. In similar cases creatine retention has been found by us profoundly affected. In this case there was 100% retention of creatine, and the highest creatine excretion on any of the three days of the creatine clearance test was 162 mg. Not only had the amputations not been followed by creatinuria, but where creatinuria was expected, the amputations, by removing improperly functioning muscles, prevented its occurrence. On the other hand, only 250 mg. of creatinine was excreted in 24 hours, and in the other three cases the excretion was likewise diminished, in one being as low as 85 mg. per 24 hours. This is consistent with the conception that the quantity of creatine excreted is related to the muscle mass.

In all of the nine cases with lesions of the cervical spinal cord there was a diminished output of creatine, ranging from 375 to 900 mg. in 24 hours. There was some correlation with creatine retention.

In 17 cases of midthoracic lesions, despite the fact that creatine retention was normal, there was a diminished output of creatine, ranging from 87 to 900 mg. In 12 cases of injury to the lower cord and cauda equina there was diminished output of creatine, ranging from 375 to 850 mg., with a median of 635 mg. There was no correlation with creatinuria. In 14 cases of hemiplegia and 3 cases of cerebral crural paraplegia the output of creatinine ranged from 490 to 1,310 mg., with a median of 787 mg., although in all of these cases there were no instances of defect of creatine retention. In six cases of late residuals of anterior poliomyelitis and in nine cases of anterior rhizotomies, in all of which creatine retention was defective, the excretion of creatine ranged from 100 to 1,212 mg., with a median of 400 mg. There was no correlation with the degree of creatine intolerance. This would suggest that diminished creatinine excretion is correlated not only with muscle mass, but also with immobility of muscles paralyzed by lesions of both upper and lower neurones.

CONCLUSIONS

1. Creatine intolerance occurs in lesions of the spinal cord only when the function of muscles is defective by reasons of a concomitant lower neurone lesion.

2. It is present after anterior rhizotomy and in severe residuals of anterior poliomyelitis.

3. It is not found in severe hemiplegia or crural paraplegia of cerebral origin.

4. The amount of creatinine excreted is related to the mass of muscle and to that amount of muscle which is immobilized by paralysis originating from both upper and lower motor neurone lesions.

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SUCCINYLCHOLINE CHLORIDE IN ELECTROSHOCK THERAPY

I. Clinical Use

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THE PREVENTION of the complications of electroshock therapy has long been a serious problem in psychiatry. The treatment of older patients has been particularly dangerous because of the high incidence of osteoporosis, which makes the patient more susceptible to fractures, and cardiovascular disease, which makes the patient more sensitive to asphyxia. The muscle-relaxing drug curare has been extensively used since 1940,[1] but its use has definite disadvantages. The action of the drug is prolonged, 10-40 minutes, and its histamine-like side-effects may result in arterial hypotension. It has practical limitations because its long action requires the time of extra personnel.

Recent researches * in the use of the synthetic muscle-relaxing drugs have shown that succinylcholine chloride may be useful in electroshock therapy. This drug was first found to have muscle-relaxant effect by Bovet and co-workers in 1949.[2]

It is a white odorless crystalline substance which is readily soluble in water. Aqueous solutions are clear, colorless, and stable to light and temperature change. Solutions may be sterilized by autoclaving without loss of potency; however, an alkaline pH appears to produce a chemical breakdown of the drug. The chemical formula is quite similar to that of acetylcholine. It is broken down, in vitro, by the cholinesterases probably into succinic acid and choline.

In large doses the drug has a "nicotinic" effect, bringing about a rise in blood pressure.[2] Only minimal histamine-like effects have been observed.[4]

To date, this drug has had limited clinical trial in electroshock therapy. Holmberg and Thesleff [5] have reported the results of its use in 512 treatments, with only one minor fracture occurring in this series. Bourne and associates [4] have reported its use in 33 patients. Balthasar and Sara [6] have reported its use in electroshock therapy, but the number of cases is not stated. More recently Ardis and Wyllie [7] have reported the use of this drug in 2,437 treatments and now routinely use the drug in all treatments given by them.

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The succinylcholine chloride (Anectine Chloride) used in this study was supplied by the Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y.

* References 2 and 3.

The following is a report of the use of this drug in 168 patients, who received 1,045 electroshock treatments.

METHOD

The electroshock equipment used was the following: the Rahm electroshock unit, the Lieberson brief stimulus unit, and the Reiter electrostimulator. Our indications for the use of succinylcholine were (1) previous severity of convulsions; (2) old age; (3) osteoporosis; (4) a history of previous fractures, and (5) cardiovascular disease.

All patients received premedication with atropine, 0.4 to 0.6 mg., given 20 to 60 minutes before treatment. The use of atropine in patients undergoing electrocardiographic studies will be described later.

The patient was placed on the bed without hyperextension of the spine, and sufficient thiopental (Pentothal) sodium, 60-600 mg., to induce sleep was then administered intravenously. Through the same needle 15-80 mg. of succinylcholine was then injected rapidly and the needle withdrawn. Generalized fasciculations were observed 15-30 seconds after the succinylcholine was injected, and generalized muscular relaxation then rapidly ensued. The patient was respirated for 30-60 seconds, using 100% oxygen. The electroshock was then given. It was possible, on occasion, to maintain respiration during the convulsion. If this was not possible, however, the patient was respirated after the cessation of the convulsion. In all cases adequate ventilation was

TABLE 1.—*Preshock Complicating Factors**

	No. of Patients
Hypertension: B. P. above 150/90	56
Proved cardiac disease on physical examination	17
Previous fractures (any)	16
Diabetes mellitus	3
Hemiplegia	2
Squamous-cell carcinoma of the ear	1
Glaucoma	1
Pulmonary fibrosis	1
	97

* Total number of patients, 168.

maintained until the patient had recovered from the effects of the drug. Care was exercised to prevent hyperventilation and hypocapnia, which frequently retarded the appearance of spontaneous respirations.

This procedure was varied in 38 cases by the omission of thiopental. This was done only to obtain electrocardiographic tracings and blood pressure recordings of the effect of succinylcholine alone. We felt that utilization of the muscle-relaxant drug without thiopental hypnosis was undesirable because of the subjective sensation of suffocation. For this reason, it was felt that further treatments without thiopental were contraindicated.

Comparative electrocardiographic and blood pressure studies were carried out on 215 patients receiving electroshock only; thiopental and electroshock; thiopental, succinylcholine, and electroshock, or thiopental tubocurarine. These will be reported on in detail later.

RESULTS

Age.—Eighty-three of the 168 patients were over 50 years of age. Of this 83, 41 were over 60 years of age. The age range was 15 to 81 years.

Complicating Factors.—Any disease existing prior to the institution of treatment which in itself might result in complications of treatment was considered a complicating factor.

Fifty-six patients were found to have a blood pressure of above 150/90. This was considered to represent moderate to severe vascular disease. On routine exami-

nation cardiac disease was found in 17 patients. This was due to rheumatic heart disease in 3 patients, old myocardial infarctions in 3 patients, and very severe hypertensive cardiovascular disease in 12 patients.

Sixteen patients had had previous fractures. These were, in the main, due to falls, although in four patients they were sustained during the course of previous courses of electroshock.

Four patients with known neurological disease were treated. These comprised one patient with mild tabes dorsalis; two with diabetes, one with hemiplegia and the other with diabetic neuropathy, and one patient with hemiplegia resulting from severe cerebrovascular disease. No accentuation of neurological signs or symptoms was noted. One patient had advanced squamous-cell carcinoma of the ear, and one

TABLE 2.—*Data on Treatment*

Number of patients treated	168
Number of treatments	1,045
Average number of treatments per patient	6
Range of number of treatments per patient	1-30

TABLE 3.—*Data on Dosage*

Dosages

	No. Patients	Average Dose per Pt., Mg.	Average Dose Mg./Kg.
Thiopental	123	117.9	1.89
Succinylcholine	136	25.7	0.42

Increased Dose Necessary

	No. Patients	Average Initial Dose, Mg.	Average Final Dose, Mg.	Difference, Mg.
Succinylcholine	34	27	34.8	7.8

patient had severe glaucoma. Severe pulmonary fibrosis with inactive tuberculosis and acute bronchitis was a complicating factor in one patient.

Treatment.—One hundred sixty-eight patients received a total of 1,045 electroshocks, for an average of 6 treatments per patient. The number of treatments ranged from 1 to 30.

Dosage.—Although Holmberg and Thesleff [5] report the use of thiopental and succinylcholine mixed in a single syringe, we felt that this was not the technique of choice; thiopental sodium in aqueous solution is alkaline (pH 10.5). Succinylcholine is reported to decompose in solutions of pH 9.5 or over. Britton and Volpitto [6] have reported reduced potency of succinylcholine when mixed with thiopental for longer than five minutes. We also felt that the short action of succinylcholine should coincide with the relatively longer hypnotic action of thiopental.

Of the 168 patients treated, detailed records were obtained on 136. Of this latter group, thiopental was given to 123 patients. The range of dosage was 60 to 600 mg. The average dose per patient was 117.9 mg. in a 2% solution. The average dose per kilogram was 1.89 mg. Older patients usually required a smaller dose of thiopental.

All the 136 patients were given succinylcholine. The average dose per patient was 25.7 mg., which is slightly higher than that reported by Holmberg and Thesleff.[5] The average dose per kilogram was 0.42 mg.

For 34 patients an increased dose was necessary. The initial average dose was 27 mg. The final average dose was 34.8 mg., with a difference of 7.8 mg. This increase in dose was usually necessary in large muscular patients. The majority of patients did not require a dosage change. It would therefore seem apparent that tachyphylaxis did not occur.

Severity of Convulsions.—The usual initial convulsion was mild or very mild. In some patients convulsions varied in intensity because of difference in the technique of the administrators of the drugs. These differences were usually slight.

Those patients whose initial dose of succinylcholine was not adequate had strong convulsions. With an increase in dose, usually 5-10 mg., the severity of the convulsion was adequately reduced.

TABLE 4.—*Severity of Convulsions*

Without Dosage Change	
Variable	47
Very mild	18
Mild	26
Moderate	7
Strong	2
Not recorded	2
With Dosage Change	
Variable	34
Total no. of patients	136

TABLE 5.—*Duration of Apnea*[*]

No. patients apneic	100
Range, min.	0.5-10
Average duration of apnea, min.	1.9

[*] Total number of patients, 136.

Apnea.—Apnea occurred in 100 of the 136 patients. The average duration of apnea was 1.9 minutes, with a range of 0.5 to 10 minutes. The maximum value occurred in two patients, and in no other patient did the apnea exceed five minutes. In 36 patients no cessation of respiration was noted. Duration of apnea was measured from the end of the convulsion to the point where adequate spontaneous respiration had taken place.

Complications.—Only three complications of treatment have occurred. The first was due to presumed excessive manipulation of the head following the treatment in this patient. A 10-minute period of apnea occurred, and the patient subsequently complained of radicular pain over the distribution of the fourth and fifth cervical nerves on the right. X-ray examination of the cervical spine showed a fracture of the right transverse process of the fourth cervical vertebra. The second complication was mild aspiration pneumonia due to aspiration of saliva. This patient salivated excessively, owing to an inadequate dose of atropine. A third complication developed when a patient with a history of asthma aspirated a small amount of vomitus

and subsequently developed atelectasis of the right lung. Prompt bronchial aspiration, inflation of the atelectatic lung, and antibiotic therapy resulted in complete disappearance of symptoms and x-ray findings in 24 hours.

No fractures occurred in the group during therapy. After the discontinuance of the use of the drug, however, fractures occurred in two patients with the next treatment.

Time.—While treating a large group of patients in the Butner State Hospital, the factor of speed was most important because of time limitations of personnel. When two physicians worked as a team, it was possible to treat one patient every six minutes. When one physician worked alone, eight minutes for each patient was required.

Although the time required for individual electroshock treatments is not in itself important, the over-all effect manifests itself by increasing the number of patients who may safely receive electroshock.

COMMENT

The results of this series indicate that succinylcholine has distinct advantages over previously used muscle-relaxing agents. The most important is its short duration of action coupled with the near-total muscular relaxation. These factors are extremely important in its use with electroshock because of the lessened danger of complications occurring during prolonged periods of apnea and subsequent weakened intercostal activity. Complete abolition of muscular contractions during the treatment can as well be carried out, thus minimizing or abolishing the dangers of the occurrence of fractures. This cannot be readily done with longer-acting drugs, since the patient on occasions may complain of weakness for long periods after he awakens. It is also possible to treat a large number of patients, since only one-fourth the time is needed to carry out the procedure as would be needed for other drugs, such as curare or decamethonium (Syncurine).

Another advantage is the lack of adverse effect on blood pressure. This will be discussed in detail in a later publication.

SUMMARY

One hundred and sixty-eight patients were given 1,045 electroshock treatments using succinylcholine chloride.

Periods of apnea, averaging 1.9 minutes, were observed during the entire series of treatments, with the longest period lasting for 10 minutes.

In three cases complications of treatment were observed which were due in part to anesthetic technique, and not to the drug.

No fatalities were observed in this series.

Dr. James Murdoch, Dr. M. Vitols, and Dr. E. Sedricks, of the Butner State Hospital, Butner, N. C., assisted in carrying out this study.

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Abstracts from Current Literature

Physiology and Biochemistry

FORMATION OF AMMONIA IN BRAIN EXTRACTS. J. A. MUNTZ, J. Biol. Chem. **201**:221, 1953.

Acetone powder extract of dog's brain contains an enzyme system which deaminates muscle adenylic acid to inosinic acid. Adenosinetriphosphate is required for the reaction, but there is no loss of adenylpyrophosphate or apparent deamination of the polyphosphate. The enzyme system is active over a broad pH range, with an optimum at pH 7. In these respects the system differs from Schmidt's deaminase and is apparently distinct from enzymes previously described which deaminate adenosine or its phosphorylated derivatives. Because of the myokinase, which is also present, adenosinetriphosphate alone can serve as a source of NH_3 when a suitable phosphate acceptor, such as fructose-6-phosphate is added to the system.

PAGE, Cleveland.

γ-AMINOBUTYRIC ACID-GLUTAMIC ACID TRANSAMINATION IN BRAIN. S. P. BESSMAN, J. ROSSEN, and E. C. LAYNE, J. Biol. Chem. **201**:385, 1953.

Brain homogenates contain a system which transaminates γ-aminobutyric acid and α-ketoglutaric acid to succinic semialdehyde and glutamic acid. The system is reversible. It is present in rat, rabbit, and calf brain. The entire activity is in the insoluble particles of rat brain. This observation is of interest because of the recent finding of γ-aminobutyric acid in mammalian brain. Transamination between γ-aminobutyric acid and α-ketoglutaric acid is a pathway for the utilization of the former in brain, leading to the formation of succinic semialdehyde.

PAGE, Cleveland.

IPSILATERAL FACIAL REPRESENTATION IN MOTOR CORTEX OF MACAQUE. E. W. LAVER, J. Neurophysiol. **15**:1 (Jan.) 1952.

With the animal under very light ether anesthesia, Laver found it possible to elicit ipsilateral facial movements by stimulation of the cerebral cortex of the macaque. Such ipsilateral movements in the macaque are not limited to the upper facial muscles but include those of the lower part of the face as well.

The area for ipsilateral movements was found to be distinct from that for contralateral movements. Within the primary facial motor area, the region for ipsilateral movements lies lateral to that for contralateral movements, but above the subcentral dimple.

The author found that an area for ipsilateral movement can also be demonstrated in the second motor area on the superior lip of the lateral fissure. This region lies anterior to that from which contralateral facial movements are obtained.

ALPERS, Philadelphia.

EFFECTS OF INTRACAROTID DIODRAST [IODOPYRACET]. E. L. FOLTZ, L. B. THOMAS, and A. A. WARD JR., J. Neurosurg. **9**:68 (Jan.) 1952.

Experiments to study the effects of intracarotid iodopyracet (Diodrast) injection were carried out on 12 monkeys, 4 cats, and 10 humans. From their studies the authors conclude that iodopyracet is far from an ideal contrast medium for cerebral angiography. Two primary effects of intracarotid iodopyracet injection were demonstrated: (*a*) a direct toxic action on the nerve cells and (*b*) a protective vasospasm, minimizing the cytotoxic effect.

Initial rapid vasoconstriction followed by longer-lasting vasodilatation was demonstrated visually and photographically in monkeys. Quantitative continuous recording of spinal fluid pressure during the angiographic procedure demonstrated an initial rapid fall in pressure followed by a longer-lasting rise corresponding to the observed vasomotor changes.

Continuous recording of the electroencephalogram during intracarotid iodopyracet injection in both monkeys and humans demonstrated multiple abnormalities which seemed to be due

to a direct toxic action of the medium on the neurone. Warm solutions of iodopyracet produced less vasospasm than cool solutions. Unilateral stellate block also abolished the phase of vasoconstriction. After this protective vasospasm had been minimized by either of these means, intracarotid injection of iodopyracet then produced far greater abnormalities in the electroencephalogram.

Some type of abnormality in the electrocardiogram or the pulse rate was routinely produced in both monkeys and humans during angiography. These seem to be the result of changes in the central nervous system.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

AN INVESTIGATION INTO THE EFFECTS OF GLUTAMIC ACID ON HUMAN INTELLIGENCE. J. R. MILLIKEN and J. L. STANDEN, J. Neurol., Neurosurg. & Psychiat. **14**:47 (Feb.) 1951.

The experiment here reported was designed to test the hypothesis that the oral administration of glutamic acid to human subjects would be followed by improvement in their scores on psychologic tests of intelligence, of both verbal and performance types.

Two groups of mentally defective adults, one group of mentally defective children, and two groups of normal boys were divided each into an experimental and a control section. Before and after treatment with glutamic acid or with an indifferent substance, each subject was given verbal, performance, and personality tests. After the second test administration, each subject was transferred to the opposite section for an additional period of treatment, at the end of which the tests were administered for a third time. The results of the cognitive tests provided no evidence in favor of the hypothesis that glutamic acid improves cognitive functioning, except in one group of normal boys, for whom the findings yielded slight, but equivocal, evidence in favor of the hypothesis. The scores on the personality tests showed no improvement due to glutamic acid treatment.

ALPERS, Philadelphia.

PSYCHIATRIC ASPECTS OF ORGANIC DISEASE. JOHN W. TODD, Lancet **1**:753 (April 7) 1951.

Todd discusses briefly the organic illnesses which cause psychiatric disturbances, such as cerebral tumors, dementia paralytica, and cerebral arteriosclerosis, the manifestations of all of which may be ascribed to "neurosis." In the case of dementia paralytica this error can be serious, but less so in the case of cerebral tumors, a minority of which are susceptible of radical cure, and the error is of no consequence in cerebral arteriosclerosis. On the other hand, states the author, the wrong deduction that psychiatric symptoms are directly caused by an organic process may sometimes be reached, possibly resulting in the patient's being made a semi-invalid. The treatment should consist of reassurance about his symptoms and encouragement to live a normal life.

The author considers the significance of psychological disturbances in the etiology of organic disease, such as peptic ulcer, ulcerative colitis, numerous dermatologic conditions, rheumatoid arthritis, and even tuberculosis. He lists four reasons why it may be wrongly concluded that organic disease is caused by emotional disturbances: 1. Organic disease is often clearly responsible for anxiety. 2. Emotional disturbances are extremely common and may therefore be coincidental with organic disease. 3. A proportion of people welcome organic disease because it gives them sympathy. 4. Emotional factors may be welcomed as an explanation of the cause of a stroke, the victim feeling that it was due to his "never sparing himself."

In discussing the practical application of the deduction that emotional factors have been responsible for organic disease, the author concludes that the most likely way of doing good is offered when the patient's anxiety is unduly concerned with his disease itself, in which case reassurance may help.

The main body of the paper is concerned with the effect of bodily disease on the emotions, and the author states that any organic disease of which the subject is aware must have some effect on the mind. However, in many cases this is not of practical importance. But there are vast numbers of people affected by comparatively trivial chronic organic diseases who are unnecessarily upset by their trouble and who, in turn, unnecessarily suffer emotional bodily symptoms. He proposes the following scheme for the handling of such patients:

1. All the symptoms—not merely those relating to the organ under suspicion—should be considered. The significance of each should be explained to the patient, it being pointed out that some are due to his disease, others to the emotions, and perhaps others, such as headache, cannot be fully understood but are of no serious consequence.

2. The patient should be interviewed, at least for a period, alone, since many people are willing to talk freely only to their physician privately. Leading questions should then often be asked; otherwise, patients may never divulge their worst fears. For example, the cardiac patient may be asked whether he fears sudden death; the subject with an innocent abdominal disease whether he suspects cancer, and the patient with bronchitis whether he fears "consumption." A confident reassurance should be given if such fears are discovered.

3. A statement, suited to the intelligence and education of the patient, should be given about the results of the examinations and investigations and the conclusions reached. He should be reassured as to his future.

4. The greatest caution should be exercised in advising a permanent regimen or diet more restricted than that dictated by the immediate symptoms. The very statement "You can eat anything you like which doesn't upset you, and do anything you like which doesn't distress you" is itself most reassuring.

MADOW, Philadelphia.

Meninges and Blood Vessels

DISSECTING ANEURYSMS OF THE THORACIC AND ABDOMINAL AORTA. G. S. LODWICK, Am. J. Roentgenol. **69**:907 (June) 1953.

Lodwick discusses the occurrence, causes, clinical features, and roentgenologic features of dissecting aneurysms of the aorta and reports on 15 cases in which postmortem studies were made. The classic type is thought to be caused by idiopathic necrosis of the media of the aorta. The two most frequent sites of internal rupture are the ascending aorta a few centimeters above the aortic valve and the descending aorta near the isthmus and the ligamentum arteriosum. Extensive dissection usually results in cases of rupture at these sites. The other type of dissecting aneurysm is thought to be secondary to arteriosclerosis. Dissection may occur when the circulating blood gains access to a weakened portion of the media of the aorta through an atheromatous ulcer. Such dissecting aneurysms often remain more limited in extent, produce less typical symptoms, occur in an older age group, and do not always cause death.

Roentgenograms can be most helpful in the diagnosis of dissecting aneurysm, provided that the interpreter of the films is familiar with the clinical history and the physical findings. Sudden increase in the size of the supracardiac aortic shadow as compared with that in previous films, or a demonstrable increase in the thickness of the aortic wall, is a reliable sign of dissecting aneurysm. The thickness of the wall may often be estimated if calcification is present within the intima. Dissecting aneurysm affecting the abdominal aorta can sometimes be demonstrated indirectly by various techniques: retroperitoneal and intraperitoneal air studies, visualization of soft-tissue masses, and demonstration of displacement of viscera by the aneurysm.

WEILAND, Grove City, Pa.

MIGRAINE IN CHILDREN: A REPORT OF FIFTY CHILDREN. G. R. KRUPP and A. P. FRIEDMAN, A. M. A. Am. J. Dis. Child. **85**:146 (Feb.) 1953.

Krupp and Friedman studied 50 children with migraine under 15 years of age. The precipitating factors could not always be determined, but stress situations of various kinds were usually the principal exciting causes. Other causes were fear of failure, disappointment, rejection, unusual stimulation, and anxiety-producing situations. The commonest preceding incident was a family argument, and frequently both mother and child had attacks of migraine. Inability to express and control hostile feelings is certainly a factor in many headaches. Thirty-five per cent of the group complained of headaches before the fourth year; 84% of the parents gave a history of headache. The migraine syndrome in most children was similar to that in adults except that the headache was less severe, while abdominal complaints were more prominent.

Gastric, psychogenic, or visual symptoms often preceded the attack. Most of the headaches were frontal, temporal, and retro-orbital and became more unilateral and throbbing as the child grew older.

The children were usually of superior intelligence and good students. There was no single dynamic pattern, but a predisposition toward certain personality traits was observed. Their traits included sensitivity, cleanliness, thoroughness, and need for approval. The patients continuously presented feelings of inadequacy, excessive guilt, and a strong superego. Practically all the children had other psychogenic symptoms, such as nail biting, feeding disturbances, thumb sucking, tantrums, enuresis, phobias, and nightmares. Symptomatic treatment with a combination of ergotamine and caffeine was adequate in 60% and helpful in 85%. Prophylaxis was carried out along psychological lines. Emotional factors were discussed with the parents, and they were advised to minimize their own headaches in the presence of the child. Most of the children improved as soon as the parents were educated to the nature of the illness.

SIEKERT, Rochester, Minn.

CARCINOMA OF THE STOMACH WITH MENINGEAL CARCINOSIS: REPORT OF FOUR CASES. G. F. MEISSNER, Cancer **6**:313, 1953.

Meissner reports four cases of diffuse carcinomatosis of the leptomeninges secondary to primary carcinoma of the stomach, confirmed by autopsy. Certain particularly interesting features are noted. In Case 1 a subtotal gastrectomy had been performed for carcinoma nine years before. The diagnosis was made ante mortem by the finding of malignant epithelial cells in the spinal fluid. The spinal fluid sugar was found to be low in the two cases in which it was determined. In three of the four cases the antemortem diagnosis was probable tuberculous or influenzal meningitis, because of the meningeal signs, the cranial nerve paralyses, and the neutrophilic and lymphocytic cellular reaction of the cerebrospinal fluid.

FOLEY, Boston.

Diseases of the Brain

MEASLES ENCEPHALOMYELITIS. M. J. FOX, J. F. KUZMA, and J. D. STUHLER, A. M. A. Am. J. Dis. Child. **85**:444 (April) 1953.

This study is based on 77 cases of measles encephalomyelitis occurring during a 25-year period. The incidence of known encephalomyelitis was 1.5 per 1,000 cases of measles. The mortality in this series was 28.6%.

The ages ranged from 5 months to 32 years; 62% of the patients were from 4 to 7 years of age, inclusive. The onset of the encephalomyelitis varied from several hours to nine days after the appearance of the rash, occurring three to four days after the rash appeared in 47%.

Diminution or absence of the cough reflex was one of the earliest signs; it was present in 74%. For this reason, and because several cases of codeine intoxication were observed, the authors suggest that codeine not be used for the cough in measles. Coma and/or convulsions occurred in two-thirds of the patients who died. The cerebrospinal fluid contained from 2 to 910 cells per cubic millimeter. In 51% of patients the fluid contained less than 40 cells and in 74% less than 90 cells, per cubic millimeter. The majority of the cells were lymphocytes. The cerebrospinal fluid protein was increased in 61% of the patients.

For 65% there was response to a follow-up questionnaire. Sixty-one per cent of these patients had recovered completely. Residual symptoms in the other 39% included changes in presonality, mental deficiency, choreiform or incoordinate movements, tremor, cord bladder, and foot drop.

Pathologic study failed to identify any characteristic lesion or distribution of lesions. Grossly, the brain is hyperemic and bulges through the incised dura. Microscopic examination reveals universal distribution of changes, consisting of severe congestion and perivascular and pericellular edema. The perivascular cellular infiltrations are variable and consist mainly of lymphocytes and histiocytes. The surrounding tissue is pale in staining. Neuronal changes appear to be secondary and are present only in areas of severe cellular infiltration.

SIEKERT, Rochester, Minn.

Treatment, Neurosurgery

STREPTOMYCIN-PROMIZOLE [THIAZOLSULFONE] THERAPY OF MILIARY AND MENINGEAL TUBERCULOSIS IN CHILDREN. E. M. LINCOLN and T. W. KIRMSE, Am. Rev. Tuberc. **61**:159 (Feb.) 1950.

Lincoln and Kirmse treated 13 children between the ages of 3 months and 11 years with miliary tuberculosis and 21 children between the ages of 9 months and 11 years with tuberculous meningitis, with streptomycin combined with thiazolsulfone (Promizole). The patients with miliary tuberculosis were given 1 gm. of streptomycin daily by the intramuscular route for 120 days. The sulfone drug was given by mouth four times daily in amounts sufficient to obtain concentrations in the blood of 1 to 3 mg. per 100 cc. The daily dose varied from 1 to 8 gm. Patients with tuberculous meningitis were given 1 gm. of streptomycin daily by the intramuscular route in two divided doses. Streptomycin was given intrathecally once daily in 0.1-gm. doses until toxic symptoms or mechanical difficulties arose; the dose then was reduced to 0.05 gm. daily, or every two days, until a total of 40 intrathecal injections was completed. Thiazolsulfone was administered in the same manner as for miliary tuberculosis. Eleven patients with miliary tuberculosis and 16 patients with tuberculous meningitis survived. Three patients with meningitis relapsed; one of these died. There was little evidence of toxic reactions to the sulfone drug except for cyanosis and slight enlargement of the thyroid. Ataxia was the most constant toxic reaction to streptomycin. Early recognition of tuberculous meningitis and intensive intrathecal therapy are important factors in survival. The location of the lesion, the sensitivity of the micro-organisms, and, possibly, the age of the patient are important in the prognosis. Four of the five patients whose deaths resulted from meningitis were less than 14 months of age and in a moderately to far-advanced stage of the disease when treatment was started. Combined streptomycin and thiazolsulfone therapy appears to have improved the results and is worthy of more extensive clinical trial.

J. A. M. A.

Muscular System

STUDIES IN DISORDERS OF MUSCLE: VII. CLINICAL MANIFESTATIONS AND INHERITANCE OF A TYPE OF PERIODIC PARALYSIS WITHOUT HYPOPOTASSEMIA. F. H. TYLER, F. E. STEPHENS, F. D. GUNN, and G. T. PERKOFF, J. Clin. Invest. **30**:492 (May) 1951.

The report by several investigators in 1937 and 1938 that the paralytic attacks in periodic paralysis were associated with depressed serum potassium values led to the conclusion that the disorder is the consequence of a fault in the regulation of serum potassium levels. Later, Talbot summarized the data concerning 400 cases of periodic paralysis. The disorder has usually been referred to as familial, or family, periodic paralysis. It seems best, as Talbot pointed out, to call the disease periodic paralysis, specifying the hereditary nature of the disorder when it is genetically determined and referring to the other cases as sporadic, the mechanism involved being specified where it is known. Talbot concluded that the syndrome probably represented a clinical entity due to a single metabolic dysfunction.

In the present study of a kindred in which 33 cases of clinically typical periodic paralysis were known to have occurred, the authors observed no striking hypopotassemia during attacks in the patients whom they studied in detail. This led them to an analysis of the genetic pattern in this kindred and a reevaluation of the data in this disorder. They studied methods of precipitating attacks, the effect of administering glucose or glucose and insulin, the effect of exercise and of enforced rest, and the correlation of these factors with serum potassium, sodium, magnesium, and phosphate levels, and with the blood glucose level. Gross and microscopic examinations of biopsy material from skeletal muscle, as well as determination of its glycogen content, also were carried out.

Tyler and his co-workers found that clinically the disorder begins in infancy with recurrent attacks of weakness or flaccid paralysis. Some extensor weakness and enlargement of muscles are evident at all times. The attacks are most consistently produced by vigorous exercise followed by complete rest. No correlation of the attacks with the serum potassium or other electrolyte concentrations could be established.

An unusual pathologic picture of vacuolation of scattered muscle fibers was found in biopsy material. Neither fat nor glycogen could be demonstrated in the vacuoles, and it is presumed that they contained only edema fluid.

The pattern of inheritance is that characteristic of a simple Mendelian dominant trait with complete penetrance. ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

FULL-COLUMN TECHNIQUE IN LUMBAR DISK MYELOGRAPHY. L. MALIS, C. M. NEWMAN, and B. S. WOLF, Radiology **60**:18 (Jan.) 1953.

Malis, Newman, and Wolf feel that the use of 3 cc. of ethyl iodophenylundecylate (Pantopaque) in lumbar myelography, as practiced in many institutions, is responsible for many of the failures attributed to this examination. They present sketches and reproductions of roentgenograms to illustrate how a thin film of the opaque medium may cause false defects and may fail to demonstrate true defects in the lumbar region of the spinal canal. Only the ventral portion of the thecal sac is filled when the patient lies in the prone position. Deformities of the nerve root pouches may not be visualized because they lie posterolateral to the oil level. The authors believe that the use of 3 cc. of ethyl iodophenylundecylate is simply a practice carried over from the use of iodized oil U. S. P. The iodized oil was very difficult to remove by aspiration and was absorbed very slowly. Ethyl iodophenylundecylate may be aspirated with ease, is relatively nonirritating, and is absorbed more rapidly than iodized oil if any is left behind.

The authors recommend the injection of enough ethyl iodophenylundecylate to fill the lower end of the thecal sac to a level above the fourth lumbar interspace when the patient stands erect. By this method the thecal sac is represented in the roentgenograms by an opaque column. Defects caused by herniated intervertebral disks are demonstrated in profile. It is necessary to take anteroposterior, lateral, and oblique roentgenograms routinely. If a defect is seen fluoroscopically, the patient may be turned in an appropriate oblique position so that the defect is demonstrated most satisfactorily in the roentgenogram. The authors believe that any peripheral defects in the opaque column are real ones when this method is used and that the problem of the "false defect" is no longer troublesome.

The method is designed primarily for the inspection of the fourth and fifth lumbar interspaces, where most herniation of the lumbar intervertebral disks occur. No mention is made of the interspaces above this level, although it is reasonable to assume that they can be examined in the customary fluoroscopic manner, if necessary, after the fourth and fifth levels have been studied.

WEILAND, Grove City, Pa.

VALUE OF THE MID-LINE TOMOGRAM IN ENCEPHALOGRAPHY AND VENTRICULOGRAPHY. M. H. POPPEL, H. G. JACOBSON, and S. B. DEWING, Radiology **60**:236 (Feb) 1953.

Poppel, Jacobson, and Dewing have been dissatisfied with visualization of structures located in the midline in air-contrast study of the cerebral ventricular system. They report 62 cases in which lateral tomograms were used to supplement the conventional examination. In the conventional examination stereoscopic lateral roentgenograms are taken both in the upright and in the recumbent position. The authors believe that the third ventricle, the aqueduct, and the fourth ventricle were shown much more clearly in the tomograms than on the conventional films. They believe that the lateral tomogram is the most important single roentgenogram made in air-contrast studies of the brain. They recommend its routine use in all such studies.

WEILAND, Grove City, Pa.

News and Comment

THE NATIONAL ASSOCIATION FOR MENTAL HEALTH, INC. FIFTH INTERNATIONAL CONGRESS ON MENTAL HEALTH

The World Federation for Mental Health announces the Fifth International Congress on Mental Health to be held in Toronto, Canada, Aug. 14-21, 1954. The theme of the Congress is Mental Health in Public Affairs. Internationally known leaders in the mental health field will present papers of general interest at the plenary sessions. There will be technical sessions, each morning, consisting of scientific papers and round-table discussions, supplemented by smaller discussion groups.

It is anticipated that many nationalities and professional groups will be represented at the Congress.

INTERNATIONAL ASSOCIATION FOR CHILD PSYCHIATRY

The International Association for Child Psychiatry will hold an International Institute on Child Psychiatry on Aug. 13 and 14, 1954, in conjunction with the Fifth International Congress on Mental Health. The theme of the Institute is Emotional Problems of Children Under Six. Members of the Institute will discuss prepared clinical case studies and research reports related to the treatment of young children. It is hoped that some broad principles of child psychiatry will emerge which will be useful to workers in this field.

Papers will be submitted from the United States and other countries which illustrate a variety of treatment methods and different professional and cultural points of view.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

It has been necessary to change the date of the Spring, 1954, examination. Although originally announced for April 29 and 30, it is now necessary to change the date to May 10 and 11, 1954. The other arrangements remain the same.